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Obstetrics

FURTHER OBSERVATIONS ON THE METABOLISM OF VITAMIN B_{12} IN HUMAN PREGNANCY

HARRY PRYSTOWSKY, M.D., ANDRÉ E. HELLEGERS, M.D., ELMA RANKE, PH.D., BRUNO RANKE, PH.D., AND BACON F. CHOW, PH.D., BALTIMORE, MD.

(From the Department of Obstetrics, the Johns Hopkins University School of Medicine and Hospital, and the Department of Biochemistry, School of Hygiene and Public Health)

OKUDA and associates[1] reported on the Vitamin B_{12} serum levels in the blood of nonpregnant, pregnant, and fetal human subjects. The data revealed that the mean level in the nonpregnant controls was 220 ± 21 $\mu\mu$g per milliliter, the pregnant 120 ± 14 $\mu\mu$g per milliliter, and the fetal 358 ± 36 $\mu\mu$g per milliliter. On the basis of these observations and those obtained in another species,[2] it was postulated that the placenta selectively absorbed vitamin B_{12}. In a subsequent report Hellegers and collaborators[3] demonstrated an increased absorption of orally administered B_{12} in pregnant humans and pregnant rats as compared to a series of nonpregnant controls. The inference was made that the fetus was the main beneficiary of the increased absorption rate. This assumption was primarily based upon the above-mentioned findings and those obtained in rat experiments which not only showed an increased B_{12} absorption in pregnancy, but also a reduced B_{12} serum level and a decreased B_{12} content in maternal target organs (liver and kidney). It was believed that such findings were best explained by the hypothesis of selective placental activity whereby fetal demand for this vitamin could be satisfied.

The present study was designed to further investigate B_{12} metabolism in human pregnancy and also to evaluate the concentrations of other relevant substances in human fetal and maternal blood. The data include determinations of B_{12}, B_{12} binding substance, glutathione, and transaminase.

Experimental Procedure

Serum B_{12} assays were performed according to the method of Skeggs.[4] The transaminase content and the capacity of the plasma to bind with B_{12} were measured by the techniques of Steinberg[5] and Davis,[6] respectively. The determination of glutathione content in erythrocytes is given in detail in a previous report.[7]

Material and Results

All observations were made upon patients delivered on the obstetrical service of the Johns Hopkins Hospital. Nonpregnant controls consisted of student nurses and patients on the gynecological wards. Two separate studies were conducted about 6 months apart. In both, the ages of the subjects were essentially the same and each group included its own controls. The parity of the pregnant individuals varied from 0 to vi. One half of the subjects were white and the other half were Negro. There was no significant difference between

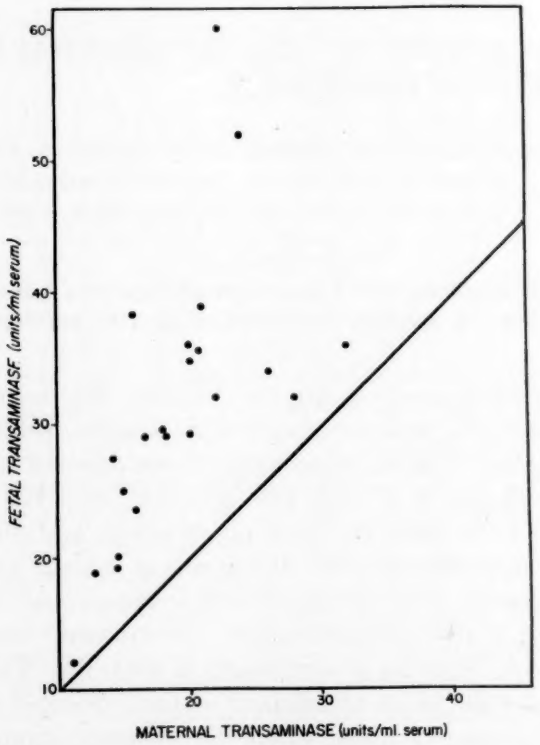

Fig. 1.—The relationship between the concentration of transaminase in maternal and in fetal serum in the human.

the two groups and many of the assays were carried out in both. Blood specimens for the various assays were obtained by venipuncture from several series of parturients at the time of delivery and from the umbilical vein of their infants. Samples from nonpregnant patients were obtained from an antecubital vein, and the sera or heparinized plasma was separated by centrifugation and used for the various chemical analyses. The data are presented in Table I.

The mean vitamin B_{12} serum level in the fetus was higher than that of the mother in both series of patients. In Group I, the maternal and fetal levels

TABLE I. DATA OBTAINED ON VITAMIN B_{12}, GLUTATHIONE, B_{12} BINDING SUBSTANCE AND TRANSAMINASE

ASSAY	PHASE	NONPREGNANT	MATERNAL	FETAL
B_{12} ($\mu\mu$g/ml. serum)	1	286 + 14.7 (25)*	180.8 + 14.7 (18)	378.1 + 38.3 (18)
	2		148.9 + 14.7 (19)	527.7 + 14.9 (19)
GSH (μM/100 ml. of RBC)	1	274 + 12.0 (20)	203.0 + 10.1 (16)	279.5 + 15.4 (16)
	2		215.0 + 12.1 (8)	248.5 + 14.6 (8)
B_{12} binding substance ($\mu\mu$g B_{12} bound/ml. serum)	1	----	3.41 + 0.05 (7)	2.75 + 0.08 (7)
SGOT (μM/ml. serum)	1	18.3 + 1.57 (19)	24.7 + 1.61 (7)	37.3 + 2.62 (7)
	2		16.72 + 0.81 (15)	29.27 + 3.28 (15)

*Numbers in parentheses refer to the number of patients studied.

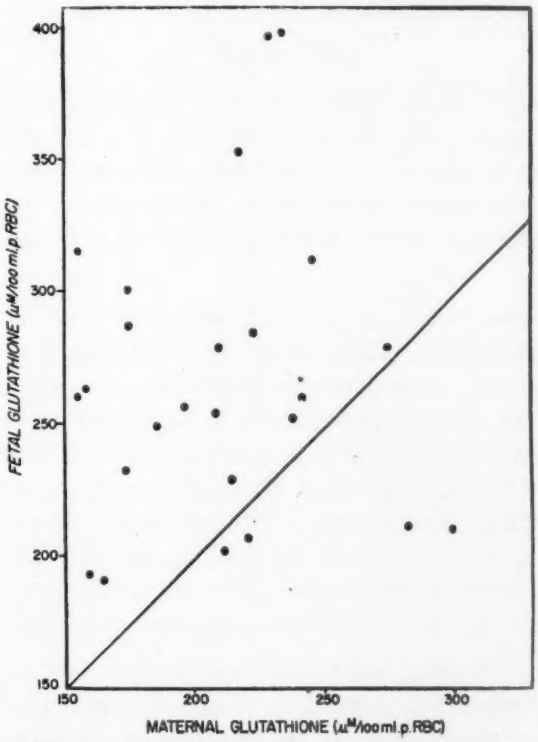

Fig. 2.—Glutathione content in fetal and maternal red blood cells.

were 180.8 ± 14.7 and 378.1 ± 38.3 $\mu\mu$g per milliliter, respectively; in Group II, 148.9 ± 14.7 and 527.7 ± 14.9, respectively. The nonpregnancy concentration was 286 ± 14.1 $\mu\mu$g per milliliter. These results are in accord with those obtained in a previous study—the maternal vitamin B_{12} content is in every case lower than that of the fetus and is lower than the nonpregnancy level.

It is also of interest to note that the glutathione (GSH) content in the erythrocytes of maternal blood was also lower than levels obtained in fetal red blood cells. Furthermore, the erythrocytes of the blood of pregnant subjects contained less GSH than the red cells of the nonpregnant controls. The values obtained for the blood of maternal, fetal, and nonpregnant subjects were 203 ± 10.1 (Group I) and 215 ± 12.1 (Group II), 279.5 ± 15.4 (Group I) and 248.5

± 14.6 (Group II), and 274 ± 12 μM per 100 ml. of RBC, respectively. The consistency of maternal-fetal GSH relationships is shown in Fig. 1. Of 24 cases, only in 3 were the fetal levels lower than those of the mother. Hence, the difference is statistically significant.

In contradistinction to the results obtained in the above two assays were the values obtained for B_{12} binding substance. The binding substance in fetal serum was almost always lower than that of the maternal serum, 341 ± 0.05 and 2.75 ± 0.08 mmcg. of B_{12} bound by each milliliter of serum.

The concentration of transaminase (SGOT) in maternal and fetal bloods paralleled the results with B_{12}. This enzyme, a reflection of pyridoxine sufficiency, was lower in the maternal sera (Group I, 24.7 ± 1.61, Group II, 16.72 ± 0.81 μM per milliliter) than in the fetal sera (Group I, 37.3 ± 2.62, Group II, 29.27 ± 3.28 μM per milliliter). In Fig. 2 a plot of maternal and fetal levels is shown; in every case the fetal content was higher than the maternal. The difference is statistically significant.

Comment

Previous studies have demonstrated that, despite an increased absorption of vitamin B_{12} in human and rat gestation, the level of pregnant women and the content in target organs of pregnant rats decrease consistently as gestation advances, whereas fetal serum levels of B_{12} are markedly higher. Presumably the fetus is the beneficiary of this nutrient since its level is considerably above that of its mother.

If these observations are of any physiological significance, then it may be expected that alterations might occur in biochemical systems involved in such metabolic processes. Since severe deficiency of vitamin B_{12} is associated with a decrease in the glutathione content in erythrocytes,[7] we were prompted to determine the concentration of this polypeptide and found a reduced concentration in maternal red cells when compared to the erythrocyte content of the fetus and nonpregnant subject. The maternal decrease may represent evidence of vitamin B_{12} deficiency in pregnancy and may be of sufficient magnitude to be of possible metabolic consequence since glutathione plays an important regulatory role in the oxidative and reductive enzymes.

The data on B_{12} binding substance demonstrate that the low vitamin B_{12} serum level in the mother was not due to some unknown pathological condition which might cause a diminution of the vitamin B_{12} binding capacity in her serum. If such were the case, the subject would have an adequate supply of vitamin B_{12} in important target organs but low serum levels. The results, however, clearly show that pregnancy does not result in the destruction of these binding substances. Hence, the low B_{12} serum level serves as an adequate guide of the B_{12} reserve.

Fetal demand for nutrients which are apparently essential for growth and development is not limited to vitamin B_{12} alone. The results of determination of the transaminase content, an indirect measure of pyridoxine, demonstrate again the possible mechanism of selective placental absorption. Thus, human pregnancy may be responsible for a relative deficiency of at least two vitamins.

Summary

The vitamin B_{12} level, B_{12} binding capacity, and transaminase content in the serum, and the glutathione content of the erythrocytes of fetal and maternal blood were determined and compared to those of a series of nonpregnant subjects. It was found that the maternal levels of these substances were lower than those from fetal sources and in nonpregnant individuals. The only exception was the data on B_{12} binding substance, in which the relationship was reversed.

We wish to acknowledge a grant-in-aid from Merck & Co., Inc.

References

1. Okuda, K., Hellegers, A. E., and Chow, B. F.: Am. J. Clin. Nutrition 4: 440, 1956.
2. Chow, B. F., Barrows, L., and Ling, C. T.: 34: 151, 1951.
3. Hellegers, A. E., and Chow, B. F.: Am. J. Clin. Nutrition 5: 327, 1957.
4. Skeggs, H. R., et al.: J. Biol. Chem. 184: 211, 1950.
5. Steinberg, D., Baldwin, D., and Ostrow, B. H.: J. Lab. & Clin. Med. 48: 144, 1956.
6. Davis, R. L., Duvall, R. C., and Chow, B. F.: J. Lab. & Clin. Med. 49: 422, 1957.
7. Ling, C. T., and Chow, B. F.: J. Biol. Chem. 202: 445, 1953.

LIVER GLUCOSE-6-PHOSPHATASE ACTIVITY IN PREGNANCY*

A Study Utilizing Albino Rats

RICHARD L. BURT, M.D., WINSTON-SALEM, N. C.
WITH THE TECHNICAL ASSISTANCE OF NANCY JULIAN, B.S.

(From the Department of Obstetrics and Gynecology of the Bowman Gray School of Medicine of Wake Forest College)

SWANSON[20] as well as Hers and de Duve[11] have identified the enzyme glucose-6-phosphatase and described procedures for its assay. Although this enzyme occurs in highest concentration in liver, lower levels of activity are detected in kidney and traces are present in intestine.[11] Glucose-6-phosphatase activity is increased in livers of alloxan-diabetic animals[1, 14] and small increments in the concentration of this enzyme result from the administration of cortisone or adrenal cortical extract in mice.[14] The enzyme is also increased in the livers of mice bearing corticotropin-secreting tumors.[19]

The results of our previous investigations have been interpreted as evidence of a diabetogenic influence of pregnancy on carbohydrate metabolism characterized by impaired peripheral utilization of glucose and resistance to insulin.[5, 6] It is conceivable that these changes are related to increased levels of glucocorticoids occurring in gestation as reported by a number of investigators. In consideration of the experimental data showing the influence of corticosteroids and experimental diabetes on glucose-6-phosphatase activity, it was of interest to study the effect of pregnancy on the concentration of this enzyme.

Material and Methods

Albino Wistar strain female rats weighing 150-200 grams were studied. They were maintained on Rockland Rat Diet ad libitum. Pregnant animals were sacrificed on the seventeenth day of gestation. After fasting 24 hours animals were decapitated and portions of liver weighing approximately 0.5 gram were rapidly removed, weighed, and homogenized in 6 ml. of 1 per cent glucose at 0° C. Duplicate 0.1 ml. aliquots of homogenate were then transferred to graduated centrifuge tubes containing 0.1 ml. of 0.1 M glucose-6-phosphate and 0.3 ml. of 0.5 M maleate buffer at pH 6.5. The tubes were then incubated at 30° C. for one-half hour together with substrate and homogenate blanks. The reaction was stopped by the addition of 2 ml. 10 per cent trichloroacetic acid. After centrifugation, the inorganic phosphorus released was determined in the supernatant by the method of Fiske and Subbarow.[9]

*This study was supported by grants-in-aid from the Forsyth County Heart Society and Parke, Davis and Company, Detroit, Mich.

The nitrogen content of homogenates was determined by a colorimetric micro-Kjeldahl technique. Assays were made on 31 nonpregnant and 23 pregnant animals.

In additional experiments progesterone* (25 mg. daily for 5 days) or estrone† (5 mg. daily for 5 days) was administered subcutaneously to individual groups of 3 rats. A single control rat for each group of 3 experimental animals was not treated but fasted and sacrificed with the experimental animals on the sixth day. Glucose-6-phosphatase activity was assayed on these animals as described.

Observations

The concentration of glucose-6-phosphatase was found to be significantly decreased in pregnancy. For nonpregnant animals, the mean value observed was 6.98 ± 1.10 mg. phosphorus per gram of liver tissue while that for animals at the seventeenth day of gestation was 5.25 ± 1.23 mg. per gram. Despite considerable variance in enzyme activity in both experimental and control animals, statistical analysis of these data by Fisher's "t" test shows a highly significant difference of the means ($P = < 0.001$). The nitrogen content of liver tissue was found to be remarkedly constant in both pregnant (27.9 mg. of nitrogen per gram) and control animals (27.6 mg. per gram). Otherwise expressed, these values represent 17.4 and 17.3 per cent protein for pregnant and control animals, respectively. These data are shown in Table I. Progesterone and estrogen at the dosage employed were without demonstrable effect on the activity of glucose-6-phosphatase.

TABLE I

	NO.	MG. PHOSPHORUS PER GRAM LIVER	σ	RANGE (MG. PHOSPHORUS PER GRAM)	MG. NITROGEN PER GRAM LIVER	σ	% PROTEIN
Pregnant	23	5.25	±1.23	3.58 – 8.77	27.9	±4.6	17.4
Control	31	6.98	±1.10	5.12 – 9.75	27.6	±3.8	17.3

Comment

The observations presented indicate that gestation in the rat is associated with a decrease in the activity or concentration of liver glucose-6-phosphatase. This is evidenced by a decrement in the amount of inorganic phosphorus split from the hexose phosphate ester in the assay method employed, the decrease in active concentration of enzyme amounting to about 24 per cent of the normal mean value for nonpregnant animals. At the variance observed, the differences of the means between pregnant and control animals were found to be highly significant.

The change in concentration of glucose-6-phosphatase appears to be real and not related to cellular hydration phenomena as indicated by the absence of significant change in nitrogen content in tissue from the two groups of animals studied (pregnant, 17.4 per cent; control, 17.3 per cent). The decrease in enzymatic activity in pregnancy thus occurs with constant protein content, and presumably constant active protoplasm, of the liver tissue studied. Whether the decrease in apparent enzyme activity is actually based on smaller amounts of phosphatase present per unit of tissue or is the result of inhibition of enzyme present is not known. It is possible that endocrine influences of pregnancy could result in such decreased enzymatic activity, although our preliminary estrogen and progesterone data suggest that these hormones are not

*The aqueous suspension of progesterone was supplied through the courtesy of S. E. Massengill Company, Bristol, Tenn.

†The aqueous suspension of estrone was furnished by Eli Lilly and Company, Indianapolis, Ind.

responsible for the change observed. Factors causing these differences in enzyme-substrate relations must await further study, not only in relation to pregnancy, but in other situations where hormonal influences have been shown to affect the activity of the phosphatase studied as in experimental diabetes and corticosteroid administration.

Glucose-6-phosphatase, acting on the 6-phosphate ester, appears to be the agent responsible for the release of glucose from the liver to the peripheral and hepatic blood. This enzyme may thus have an important regulating function in controlling the release of hepatic glycogen and other precursors of glucose-6-phosphatase. The decrease in enzymatic activity in pregnancy that we have observed could permit the accumulation of hepatic glycogen, an interpretation suggested by our previous finding of small but significant increments in the glycogen content of livers of pregnant animals.[7] By limiting glucose-6-phosphate hydrolysis, the reactions concerned with glycogen degradation to glucose could be slowed by accumulation of the 6-phosphate ester, thus tending to promote glycogen conservation.

The lower phosphatase activity may be related to the low normal fasting blood sugar concentration in human pregnancy observed by many investigators.[8, 12, 13, 15, 18] Such a decrease in enzymatic activity in the liver could result in lower glucose levels of peripheral blood by reason of a lag or decrease in the rate of glycogen release. No data are at present available, however, concerning gestational changes in hepatic glucose-6-phosphate in human pregnancy.

Increased steroid levels under experimental or pathologic conditions elevate glucose-6-phosphatase activity[14, 19] and in human pregnancy plasma levels of corticosteroids are increased either by placental secretion or adrenal activity.[2, 3, 4, 10, 16, 17] The status of steroid changes in rat pregnancy is not known, but the change in phosphatase activity that we have observed is opposite to that found by the experimental technique of ACTH or cortisone administration. It is possible that in the complex hormonal milieu of pregnancy factors other than corticosteroids may dominate the changes in enzyme activity, and our data are not necessarily inconsistent with either experimental data or the observations of increased corticoids in human gestation. Although steroid influences have been considered inferentially to be responsible for changes in the peripheral utilization of glucose and insulin resistance, other factors, as noted, may determine the changes in hepatic metabolism of carbohydrate.

Finally, fasting has been shown to affect glucose-6-phosphatase activity[14] and it appears that errors in the interpretation of enzyme assays could arise without appropriate control of food intake of animals. No dietary control was exercised in our experiments, although all animals were fasted 24 hours prior to sacrifice. In view of the heightened metabolism of gestation, the pregnant state should augment the metabolic effect of a fasting period. As our data show decreases rather than increases in enzyme activity, it is considered unlikely that decreased food intake is responsible for the changes observed in pregnant animals.

Summary

1. Pregnancy is associated with a decrease in glucose-6-phosphatase activity in the rat. The nitrogen concentration of liver is unchanged.

2. The possible relation of alterations in glucose-6-phosphatase activity to peripheral blood sugar concentration and hepatic glycogen storage in pregnancy is discussed.

References

1. Ashmore, J., Hastings, A. B., Nesbett, F. B., and Renold, A.: J. Biol. Chem. **218**: 77, 1956.
2. Assali, N. S., Garst, J. B., and Voskian, J.: J. Lab. & Clin. Med. **46**: 385, 1955.
3. Assali, N. S., and McKay, E.: Clin. Res. Proc. **5**: 189, 1957.
4. Bayliss, R. I. S., Browne, J. C. M., Round, B. P., and Steinbeck, A. W.: Lancet **1**: 62, 1955.
5. Burt, R. L.: Obst. & Gynec. **7**: 658, 1956.
6. Burt, R. L.: AM. J. OBST. & GYNEC. **74**: 551, 1957.
7. Burt, R. L., and Kimel, C. A.: AM. J. OBST. & GYNEC. **74**: 295, 1957.
8. DeCamp, A. L.: AM. J. OBST. & GYNEC. **37**: 285, 1939.
9. Fiske, C. H., and Subbarow, Y.: J. Biol. Chem. **66**: 375, 1925.
10. Gemzell, C. A.: J. Clin. Endocrinol. **13**: 898, 1953.
11. Hers, H. G., and de Duve, C.: Bull. Soc. chim. biol. **32**: 20, 1950.
12. Hurwitz, D., and Jensen, D.: New England J. Med. **234**: 327, 1946.
13. Johnson, D. G., and Bonsnes, R. W.: J. Clin. Invest. **27**: 745, 1948.
14. Langdon, R. G., and Weakley, D. R.: J. Biol. Chem. **214**: 167, 1955.
15. Lund, C. P., and Wesse, W. H.: AM. J. OBST. & GYNEC. **65**: 815, 1953.
16. Meyerheim, G., and Hübener, H. J.: Naturwissensch. **39**: 482, 1952.
17. Migeon, C. J., Prystowsky, H., Grummbach, M. M., and Byron, M. C.: J. Clin. Invest. **35**: 488, 1956.
18. Rowe, A. W., Gallivan, D. E., and Matthews, H.: Am. J. Physiol. **96**: 94, 1931.
19. Shull, K. H., et al.: J. Biol. Chem. **222**: 415, 1956.
20. Swanson, M. A.: J. Biol. Chem. **184**: 647, 1950.

THE BLOOD GASES, pH, AND PLASMA ELECTROLYTES OF THE SOW AND FETAL PIG AT 106 DAYS OF PREGNANCY*†

JOHN N. CUMMINGS, PH.D., AND IRWIN H. KAISER, M.D.,
ST. PAUL, MINN.

(From the Department of Animal Husbandry, Institute of Agriculture, and the Department of Obstetrics and Gynecology, The Medical School, University of Minnesota)

THERE is at present little known about biochemistry of the fetal pig, despite the fact that the wealth of material from the slaughterhouse has made the pig embryo a standard of anatomical embryological information. Physiological study is made quite difficult by the large size of the pregnant sow and her considerable refractoriness to handling, which makes deep anesthesia obligatory, as well as by the large size of the uterus and the large number of fetuses in a litter.

Nevertheless, study of the physiology of pig pregnancy is of importance for several reasons. Perinatal losses in the pig are greater than those of any other domestic animal and have been demonstrated to take place at any stage of development. Virtually nothing is known of the reasons for this loss. Further, the morphology of the pig placenta is different from that of any other commonly studied species, and corresponding differences in the movement of materials across the placenta have been demonstrated.

The present report, which is clearly only a limited beginning, is concerned with the distribution of hemoglobin, blood gases, hydrogen ions, and electrolytes in the pregnant sow and the fetus, at 106 ± 1 days of pregnancy. This time was chosen because it just precedes viability, and nevertheless affords fetuses of large size.

Materials and Methods

Three Duroc and three Chester White sows were crossbred to Duroc and Chester White boars, except for one Duroc-Duroc mating. The sows were maintained under ideal conditions of housing and feed from prior to mating until operation. The date of breeding was known.

The sows, which weighed about 200 kilograms, were prepared for operation by snubbing and the intravenous administration of Nembutal. They struggled vigorously until large quantities of Nembutal, as much as 2.5 Gm. in one instance, had been given. The abdominal wall and muscles in the left flank were then infiltrated with procaine and, with the sow on her right flank,

*This study was supported by grants from the Louis W. and Maud Hill Family Foundation of St. Paul, Minn.

†Paper No. 3914, Scientific Journal Series, Minnesota Agricultural Experiment Station, University of Minnesota.

the abdominal wall incised. It was necessary to administer anesthetic concentrations of Nembutal to all but one of the sows, despite efforts to work under local anesthesia.

Blood samples were obtained from the femoral artery and uterine vein of the sow. The first large uterine vein to be found was employed; this was usually in the mid-portion of the uterus. The uterus was then incised over each fetus and 2 fetuses from each sow arbitrarily selected for sampling of blood from the umbilical vein and artery. These samples were taken early in the sequence of deliveries.

Blood was drawn into oiled heparinized syringes which were capped and placed in ice water. When all the studies to be done on fresh whole blood were completed, the blood was centrifuged and plasma drawn off for further electrolyte studies.

pH was measured in a glass electrode contained in a water jacket at 38° C. with the use of a Cambridge Research model pH meter. Carbon dioxide and oxygen content were measured by the method of Scholander and associates[1] on whole blood. Plasma carbon dioxide content, carbon dioxide pressure, and bicarbonate were calculated, assuming a pK′ of 6.10. Hemoglobin was determined by measuring the total iron of concentrated hemoglobin solutions. After the plasma had been drawn off the centrifuged red blood cells, the blood was reconstituted to its original volume with distilled water, and the resulting solution was used for iron determination. This method was an improvisation necessitated by the presence of a contaminant in the distilled water which rendered spectrophotometric determination of hemoglobin grossly inaccurate during the period of these experiments. The results are approximations, but values obtained on pairs of blood (i.e. on umbilical vein as compared with umbilical artery) check well.

Sodium and potassium were determined by flame photometry, by standards containing appropriate concentrations of both sodium and potassium. Calcium and magnesium combined were measured by the chelation method of Sobel and Hanok.[2] Chloride was determined by a micro-adaptation of the methods of King and Bain[3] and Stiff.[4] Protein was determined by a modification of the Bromsulphalein method suggested by Nayyar and Glick.[5] Subsequent restudy of this method as it was modified in our laboratory, in the very low ranges found in the present study, has shown it to have a large range of error, but mean values are likely to be satisfactory approximations. Phosphate was determined by a modification of the method of Taussky and Shorr.[6] Lactate was measured by a micro-modification of the method of Barker and Summerson[7]. Pyruvate was determined by the technique of Friedemann and Haugen.[8] Details of these methods have been published elsewhere.[9, 10]

Results

All the sows were examined at 106 ± 1 days of pregnancy. Notes from the individual protocols are as follows:

No. 1 was quiet during the procedure. The left tubal end of the uterus was identified and venous maternal blood obtained. The fetuses were then removed seriatim from left to right. Umbilical blood was taken from the first and third left fetuses with membranes intact. The second left fetus and the third fetus from the uterine bifurcation on the right were blighted. There were 11 living fetuses, which were not weighed. All were in excellent condition after delivery.

No. 2 was obviously cyanotic during the procedure. The uterus was difficult to palpate but the left cornual end was found and blood drawn from a vein near it. Umbilical blood was drawn from the fetus at the tubal end in the left uterus and the cervical

end of the right uterus. There were 12 fetuses in all, ranging from 560 to 1,060 grams. The fetuses sampled weighed 1,015 and 630 grams, respectively. All were in excellent condition.

No. 3, the Duroc sow mated to a Duroc boar, was also cyanotic during the procedure. The uterus prolapsed during struggling and was handled extensively before sampling in the effort to reposit it. Blood was taken from the left tubal end of the uterus, and from the umbilical cord of the first and third fetuses from the left cornual end. There were 16 fetuses, ranging in size from 355 to 1,165 grams, all in good condition. The fetuses sampled weighed 1,165 and 1,065 grams, respectively.

No. 4 was satisfactorily anesthetized. The cervical end of the uterus was identified and blood drawn from a vein there. The fetuses in the right uterus were then removed, umbilical samples being taken from the first and fourth fetus on the right from the cervical end. There were only 4 fetuses on this side of the uterus. The left side contained 7 fetuses, 2 of them dead. Weights ranged from 745 to 1,150 grams. The fetuses sampled weighed 1,150 and 1,060 grams, respectively.

No. 5 was satisfactorily anesthetized. The cervical end of the uterus was found and venous blood obtained there. Twelve fetuses were found, 6 in each horn of the uterus. On the left, they were removed beginning at the cervical end, and blood samples obtained from the first and last. Fetal weights ranged from 755 to 1,180 grams, and the fetuses sampled both weighed 1,060 grams. All were in good condition except a very small resorbing fetus on the left.

No. 6 was operated upon principally under local anesthesia. The tubal end of the uterus was identified on the left and venous blood obtained there. Fetuses were then removed beginning at the left tubal end and continuing seriatim past the bifurcation. Three fetuses were found on the left and 9 on the right. They ranged in weight from 790 to 1,240 grams and were all in good condition. The first fetus on the left and the first on the right (at the cervical end) were sampled. They weighed 1,210 and 1,150 grams, respectively.

In no case was there any evidence of uterine contraction during these procedures.

The results of the chemical determinations on these blood samples are presented in Tables I and II.

TABLE I. pH, CARBON DIOXIDE, OXYGEN, AND HEMOGLOBIN CONCENTRATIONS, CARBON DIOXIDE PRESSURE AND OXYGEN SATURATION IN THE BLOOD OF 6 SOWS AND 12 FETAL PIGS, AT 106 ± 1 DAYS OF PREGNANCY

	pH	PLASMA CO_2 (MM./L.)	PLASMA pCO_2 (MM. Hg)	O_2 (VOL. %)	Hgb. (GM. %)	O_2 SATURATION (%)
Sow femoral artery						
Mean	7.39	27.0	44.3	12.0	10.2	88
Range	7.29-7.47	22.3-30.3	37.6-56.0	9.1-14.2	8.8-12.8	77-98
Sow uterine vein						
Mean	7.35	28.2	50.3	9.2	10.3	67
Range	7.25-7.45	23.9-30.4	42.0-59.9	8.4-10.7	8.4-12.2	57-74
Umbilical vein						
Mean	7.37	31.7	53.5	7.5	9.6	59
Range	7.30-7.44	28.4-33.6	44.0-65.9	5.1- 9.1	8.3-11.3	41-74
Umbilical artery						
Mean	7.34	33.1	60.6	3.8	9.5	30
Range	7.25-7.39	30.1-35.7	51.0-74.2	1.7- 4.7	7.8-11.1	14-38

The values in Table I for pH and oxygen saturation would be higher and for pCO_2 lower if sows 2 and 3 were omitted, but in view of the small number of animals this does not seem justified. It appears clear that the low pH and oxygen saturation values found in these two sows were produced by the circumstances of operation and blood sampling. The omission of the results

on these animals and their fetuses, however, would not alter the relationships between fetus and sow, since the fetal values are biased in the same direction as the maternal.

It will be noted in Table I that the pH and pCO_2 of the umbilical vein blood were higher than those of the uterine vein blood, and the oxygen content lower. Since the fetal pigs consistently were found to have a lower hemoglobin than the sow, the umbilical vein saturation was lower than that of the uterine vein because of its lower oxygen content.

The acute changes in respiratory components noted in the samples from No. 2 and No. 3 do not appear to have corresponding alterations in the distributions of electrolytes, except for a very low bicarbonate value found in sow No. 3.

The differences between sow and fetus in regard to sodium and potassium, as may be seen in Table II, are within limits of error of the methods employed. The 2 fetuses of sow No. 4 were both found to have very low potassium concentrations, for which we have no explanation. If they are excepted, the mean fetal potassium concentration is 4.5 mEq. per liter. The combined calcium and magnesium concentration in every fetus exceeded that of its sow; this is a significant difference. The cation totals, as may be seen in Table III, were slightly higher in sow blood, but the difference is not significant.

TABLE II. CONCENTRATIONS OF ELECTROLYTES (MEQ. PER LITER) IN PLASMA OF 6 PREGNANT SOWS AND 12 FETAL PIGS AT 106 ± 1 DAYS OF PREGNANCY

	SODIUM	POTASSIUM	CALCIUM +MAGNESIUM	CHLORIDE	BICARBONATE	PROTEIN	PHOSPHATE	LACTATE
Sow femoral artery								
Mean	145.3	4.3	6.3	101.0	25.6	20.9	3.8	6.0
Range	143.2-148.0	3.8-4.7	5.7-6.7	97.9-103.1	20.9-28.6	19.2-22.2	3.5-4.5	3.3-11.5
Sow uterine vein								
Mean	146.0	4.7	6.3	100.6	26.6	20.8	3.8	6.3
Range	142.6-148.1	4.3-5.0	5.7-6.7	97.7-103.7	22.3-28.6	19.0-22.1	3.5-4.4	3.1-11.8
Umbilical vein								
Mean	143.0	4.2	6.9	93.2	30.1	2.9	3.5	6.4
Range	139.1-147.1	2.6-5.2	6.2-7.9	90.4-96.2	27.1-32.1	2.5-4.4	2.8-4.4	4.8-8.7
Umbilical artery								
Mean	143.0	4.0	6.9	92.2	31.2	3.0	3.4	6.3
Range	139.3-146.2	2.6-5.0	6.2-8.0	88.6-95 3	28.6-34.0	2.5-4.6	3.0-4.5	4.5-8.3

TABLE III. TOTALS OF DETERMINED IONS (MEQ. PER LITER) IN 6 PREGNANT SOWS AND 12 FETUSES AT 106 ± 1 DAYS OF PREGNANCY

	CATIONS	ANIONS
Sow femoral artery, mean	155.9	157.4
Sow uterine vein, mean	157.0	158.1
Umbilical vein, mean	154.1	136.2
Umbilical artery, mean	153.9	136.1

The situation is quite different in regard to the anions. Fetal lactates and phosphates were essentially the same as those of the sow. There were, however, major differences in regard to protein, chloride, and bicarbonate. The protein concentration in pig fetal blood at this stage of pregnancy was very low as compared to that of the sow. The use of a fixed value of 2.43 for conversion from grams per 100 ml. to milliequivalents per liter results in an underestimate since the protein present in the fetuses was almost entirely albumin. Nevertheless there was a large difference between the protein anion concentrations of sow and fetus.

Fetal bicarbonate was quite high both absolutely and relative to that in the sow, and chloride was correspondingly reduced. The total of the chloride and bicarbonate ions in maternal artery and umbilical artery, respectively, were 126.6 and 123.4 mEq. per liter.

The mean concentration of pyruvate was 2.9 mg. per cent in the sows, with a range of 2.1 to 3.3, and 3.5 mg. per cent in the fetuses, ranging from 2.1 to 6.4 mg. per cent. However, the mean concentration in umbilical artery blood was 2.9 mg. per cent, while that in umbilical vein blood was 4.1 mg. per cent. In every fetus the vein concentration exceeds that in the umbilical artery, so that the difference, although small, is significant. No such difference was observed between the uterine vein and femoral artery blood of the sow. These concentrations, since they are all much less than 1 mEq. per liter, are not important to electrolyte distributions.

Under these circumstances, the total determined anions in the fetus did not equal either the determined cations or the determined anions of the sow. A small part of this deficit, as indicated, may be accounted for by the underestimate of the anionic equivalence of protein in the fetus, but some other unidentified anion must have been present. Furthermore, the anion must have been present in much higher concentration in the fetal blood than in the maternal, since there was actually a small excess of determined anions over cations in the sow's plasma.

Comment

Any discussion of these results must be prefaced by the observation that they refer to nonphysiological conditions. General anesthesia was necessary before the sows would tolerate the handling required for fetal sampling, and changes consequent to the depression of respiratory exchange were inevitable. The pig often spontaneously assumes the lateral recumbent position, so that alterations due to position, such as those which occur in the sheep, a species which sleeps and rests in the ventral recumbent position most of the time and which experiences circulatory and respiratory changes in the lateral recumbent,[11] are not likely to be present.

The blood samples were obtained rapidly, and there is no reason to suppose that the technique of sampling has in any way distributed the electrolyte concentrations, or the relationships of the concentration of gases. Absolute carbon dioxide levels are probably elevated and oxygen somewhat reduced by the anesthesia. The mean oxygen saturation of the sows was 88 per cent, and carbon dioxide pressure 44.3 mm. Hg. This may be compared with values of 83 per cent and 34.3 for the pregnant ewe at 142 days of gestation in the lateral recumbent position under local anesthesia.[9] Pregnancy lasts about 114 days in the sow and 150 days in the ewe, so that these durations of pregnancy at the time of sampling are comparable.

The hemoglobin concentration in the blood of the fetal pig in the period just before viability is less than that in the blood of the sow, and the protein concentration is markedly lower. The fetal lamb, on the other hand, reaches a level of hemoglobin approximately that of the ewe between 106 and 124 days of pregnancy,[9] and the lamb has much higher protein levels than the fetal pig throughout.[10] The oxygen saturation of the umbilical vein in the fetal pig is roughly the same as that of the term lamb, the values being 59 and 65 per cent, respectively, but the umbilical arteriovenous oxygen difference is very much greater in the lamb, being 7.1 vol. per cent as compared to only 3.7 vol. per cent for the pig. The weight of the term lamb is of course considerably greater than that of the term fetal pig.

The pH of umbilical blood in these pigs was relatively high, and indeed that of the umbilical vein was higher than that of the uterine vein blood. This relationship is different from that observed in the other species in which the pH of the fetal blood has been compared with that in the maternal blood[9, 12, 13]; in these the umbilical vein blood pH was lower than that of the uterine vein blood. The carbon dioxide pressure in the fetal pig was found to be relatively close to that in the sow, despite a high carbon dioxide content and low oxygen saturation. The bicarbonate concentration was, by the same relationship, relatively high in the fetal pig.

The cation distribution of the term fetal pig was quite similar to that found in other fetuses, relative to the maternal animal, except for the potassium which tended to be about equal to that of the sow.

The chloride concentration in the fetus was considerably less than that of the sow, counterbalancing the high bicarbonate of the fetus. Since phosphate and lactate were about equally concentrated in the sow and fetus, the very much lower protein concentration of the fetus resulted in a marked deficit of determined anions. There was a mean difference of 16.6 mEq. per liter of determined ions between the fetal anion and cation totals, and a mean difference of 21.6 mEq. per liter between determined anion totals in sow and fetal bloods. The missing anion (or anions) is presumably non-diffusable, since determined anions and cations approximately balance in the blood of the sow. As noted, the fetal bicarbonate was relatively high, and there is nothing in our data to suggest the presence of acidosis. The unidentified anion therefore does not appear to play a significant role in acid-base balance.

The significantly higher concentration of pyruvate in umbilical vein blood suggests the production of this substance in the placenta, since uterine vein and umbilical artery blood pyruvates were equal to each other and lower than that in the umbilical vein. Since fetal lactate concentration slightly exceeded maternal, the first step in fetal metabolism of this pyruvate may be its conversion to lactate. Studies of umbilical cord blood of sheep,[10] goats,[13] and man[14] in our laboratory have not demonstrated any such pyruvate relationship as this in those species.

The observation by Flexner and his co-workers[15] that the movement of radiosodium across a unit weight of the sow's placenta was about one-sixteenth of its movement across a unit weight of the goat's placenta was correlated by them with the anatomical type of placenta. As defined by Grosser,[16] the sow placenta is epitheliochorial. The epithelia of the endometrium and chorion are intact, so that diffusion between the two blood streams must occur across all the tissue layers. The goat placenta on the other hand is defined as syndesmochorial, since the chorion burrows down into the endometrial stroma in the formation of the cotyledonary buttons.

More recent anatomical studies, particularly those of Amoroso,[17] have seriously questioned the validity of Grosser's classification as a description of the area available for diffusion. Amoroso demonstrated that fetal and maternal capillaries may rise within the epithelium to a point where they are in close approximation. By strict anatomical definition, the several tissue layers may be intact, but the distance across which diffusion takes place is less than this would imply. Unfortunately, the extent of these capillary alterations is not yet fully defined, so that, although the total area for diffusion can be estimated, the mean distance is not known. Therefore, although a question can be raised as to the appropriateness of correcting for exchange on the basis of placental weight, as Flexner did, this question cannot presently be answered, nor can any more exact basis for correcting transfer rates be offered.

The steady state relationships of substances of the type determined in the present study can, however, be used to a limited extent in comparing the exchange of material across the placenta of one species with that of another.

For example, using only the figures from our own laboratory as a basis for calculation, we find that the plasma carbon dioxide pressure gradient between maternal arterial blood and umbilical vein blood was 9.2 mm. Hg for the sow, 10.2 for the goat, and 11.0 for the sheep, at 106, 138, and 144 days of pregnancy, respectively. The pig had a higher carbon dioxide content and pressure in its plasma but the pressure gradient across the placenta was smaller than for goat and sheep. In regard to pH, the corresponding values were 0.02 units, 0.07, and 0.09. It would be most valuable to have information about the oxygen pressure relationships, but only oxygen saturations have been determined and they are not necessarily comparable because of species differences in the oxygen dissociation curve.

Further, in regard to electrolytes, although the absolute level of sodium is quite high in sheep and low in man, with pigs and goats in an intermediate position, in all four species at term the fetal level is slightly lower than the maternal. The combined calcium-magnesium concentration is higher in the fetus than in the mother in all four species, but the absolute level and fetal-maternal gradient are highest in the sheep, and least in the human, with goat and pig again in an intermediate position. Potassium concentration is higher in the fetus of man, goat, and sheep than in the mother, but the concentration in the fetal pig appears to be about the same as that in the sow.

The situation in regard to anions is more complicated, since protein concentrations were much lower in the term fetus in pig, sheep, and goat than in man, and in all three of the former species a large deficit of determined anions has been found. The largest deficit was found in the fetal pig, since not only was the fetal protein concentration lowest, but there was also a large gradient of chloride between the sow and piglet.

In general it appears that, although differences among the several species are present in steady-state gradients, they are not uniformly suggestive of impediment to exchange across the pig placenta as compared with that of goat, sheep, and man.

Summary

Blood was obtained under general anesthesia from 6 sows and 2 fetuses of each, at 106 ± 1 days of pregnancy.

The pH of umbilical vein blood was found to be higher than that of the uterine vein, but lower than femoral artery blood of the sow. The carbon dioxide contents were high and the carbon dioxide pressure of umbilical vein blood higher than that in the uterine vein. Oxygen saturations were all low, presumably due to the anesthetic, so that the conditions were not physiological. The fetal-maternal relationships were presumably maintained, however. The fetal hemoglobin concentration was less than the maternal, and the umbilical arteriovenous oxygen difference quite small.

The sodium and potassium concentrations in sow and fetus were about equal. Fetal calcium-magnesium combined exceeded maternal. Fetal protein concentrations were very low, and fetal chlorides were lower than maternal. Fetal bicarbonate exceeded maternal, while lactate and phosphate concentrations were equal. Fetal pyruvate was high in the umbilical vein blood, whereas umbilical artery values equaled maternal. There was a large deficit of determined anions in the fetal blood.

References

1. Scholander, P. F., Flemister, S. C., and Irving, L.: J. Biol. Chem. **169**: 173, 1947.
2. Sobel, A. E, and Hanok, A.: Proc. Soc. Exper. Biol. & Med. **77**: 737, 1951.
3. King, E. J., and Bain, D. S.: Biochem. J. **48**: 51, 1951.
4. Stiff, H. A., Jr.: J. Biol. Chem. **172**: 695, 1948.
5. Nayyar, S. N., and Glick, D.: J. Histochem. **2**: 282, 1954.
6. Taussky, H. H., and Shorr, E.: J. Biol. Chem. **202**: 675, 1953.
7. Barker, S. B., and Summerson, W. H.: J. Biol. Chem. **138**: 535, 1941.
8. Friedemann, T. E., and Haugen, G. E.: J. Biol. Chem. **147**: 415, 1943.
9. Kaiser, I. H., and Cummings, J. N.: J. Appl. Physiol. **10**: 484, 1957.
10. Kaiser, I. H., and Cummings, J. N.: Am. J. Physiol. **193**: 627, 1958.
11. Greenberg, A., Visscher, M. B., Petersen, W. E., and Boyd, W. L.: J. Am. Vet. M. A. **101**: 417, 1942.
12. Goodlin, R. C., and Kaiser, I. H.: Am. J. M. Sc. **233**: 662, 1957.
13. Cummings, J. N., and Kaiser, I. H.: Am. J. Physiol. (In press.)
14. Kaiser, I. H., and Goodlin, R. C.: Am. J. M. Sc. **235**: 549, 1958.
15. Flexner, L. B., and Gellhorn, A.: AM. J. OBST. & GYNEC. **43**: 965, 1942.
16. Grosser, O.: Vergleichende Anatomie und Entwicklungsgeschichte der Eihäute und der Placenta mit besonderer Berücksichtigung des Menschen, Vienna and Leipzig, 1909, W. Braumuller.
17. Amoroso, E. C.: In Flexner, L. B., editor: Gestation: Transactions of the First Conference, New York, 1955, Josiah Macy, Jr., Foundation, p. 119.

RADIATION REDUCTION IN DIAGNOSTIC OBSTETRICAL RADIOGRAPHY: THE APPLICATION OF ELECTRONIC PHOTOGRAPHIC TECHNIQUES

R. M. Lowman, M.D., E. Donnellan, Ph.D., and S. Goldenthal, M.D., New Haven, Conn.

(From the Department of Radiology, The Memorial Unit, Grace-New Haven Community Hospital, Yale Medical Center)

OBLIGATED as physicians to safeguard the health of patients, radiologists have constantly investigated various procedures to reduce radiation exposure without loss of diagnostic accuracy. The predicted long-term genetic hazards and the development of somatic changes, particularly of the reticuloendothelial system, inherent in the increased production and use of ionizing radiation throughout the world, become the concern of the radiologist.

Obstetrical roentgenographic studies are particularly important from this point of view. Add to this the concept that obstetrical radiography may initiate malignant changes in the fetus and produce an increased incidence of leukemia and other malignant conditions in childhood, and the necessity for reducing the exposure dose becomes of extreme importance.[5]

Theoretical Considerations

First, it must be stressed that radiographic studies should be restricted to the cases in which such procedures will provide critical information in the solution of major obstetrical problems. The criteria for the use of radiographic investigations in obstetrics are well known and have been decisively stated by other authors.[1] Filming procedures should be revised so that techniques which yield maximum information will be retained and utilized. Critical appraisal of obstetrical filming techniques that require increased dose exposure indicates that these procedures should be discarded. Up to now the reduction of maximum radiation exposure has been achieved by combining several important physical factors:

1. Increased aluminum filtration to produce increased primary beam filtration. The use of 2.0 to 3.0 mm. of aluminum filtration serves to absorb the softer components of the x-ray beam, that are otherwise absorbed in the superficial tissues. Moreover, the softer components of the beam do not significantly contribute to the exposure of the film. Thus the use of 2.5 mm. aluminum added filtration is recommended in Handbook 60 of the National Bureau of Standards instead of the 0.5 mm. of aluminum. This added filtration reduces the skin dose of the patient by a factor of 50 per cent. Whitehouse[6] reported the ingenious use of a brass wedge filter in filming the lateral projection of the

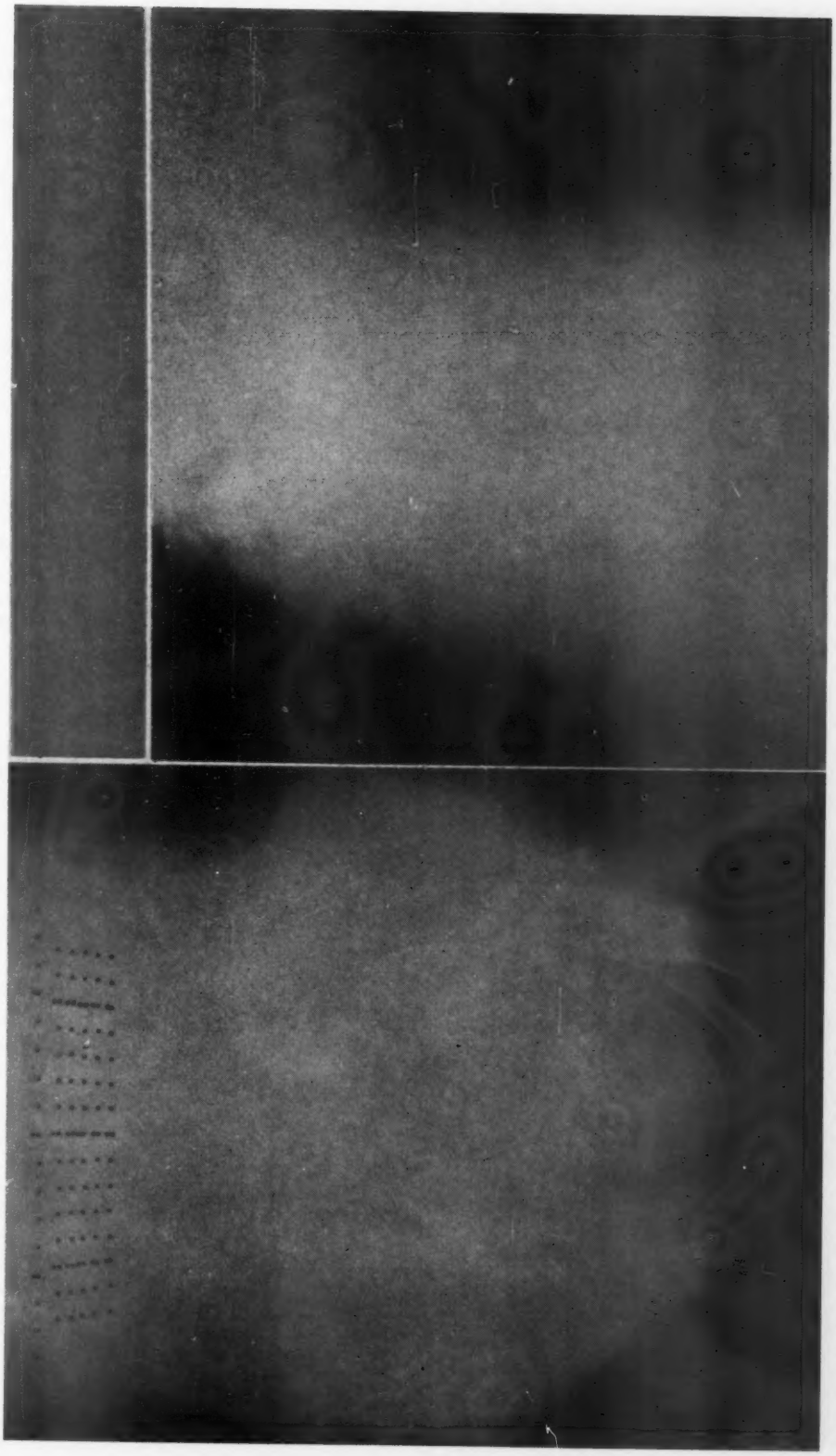

Fig. 1.—Anteroposterior and lateral pelvimetric study utilizing the deliberate underexposure technique. The details of the fetus and pelvis are largely obscured. Such a study ordinarily would be deemed inadequate for diagnostic evaluation.

TABLE I. RADIATION EXPOSURE TO SKIN, MATERNAL OVARIES, AND FETAL GONADS DURING OBSTETRICAL RADIOGRAPHY*

	PROJECTION	TECHNIQUE (KV.)	ADDED FILTER	FILM, ETC.	MAS	R RECEIVED PER EXPOSURE		
						AT SKIN	AT MATERNAL OVARY	AT FETAL GONAD
1	Anteroposterior	1 92	1 mm. AL.		120	3.8	0.48	0.76
2	Anteroposterior	2 100 kv.	3 mm. AL.	Royal blue + Radeline high speed screen	25	0.54	0.10	0.16
3	Anteroposterior	3 100 kv.	3 mm. AL.	Royal blue + Radeline high speed screen + Log-Etronic device	10	0.22	0.04	0.06
1	Lateral†	1 92	1 mm. Al.		240	13	0.62	0.11
2	Lateral†	2 100 kv.	3 mm. Al.	Royal blue + Radeline high speed screen	50	1.5	0.14	0.03
3	Lateral†	3 100 kv.	3 mm. Al.	Royal blue + Radeline high speed screen + Log-Etronic device	30	1.0	0.08	0.02

*Location of ovaries and fetal gonads is that used by Clayton, Farmer, and Warrick.[1]
†Maternal ovaries and fetal gonads lie outside primary beam.

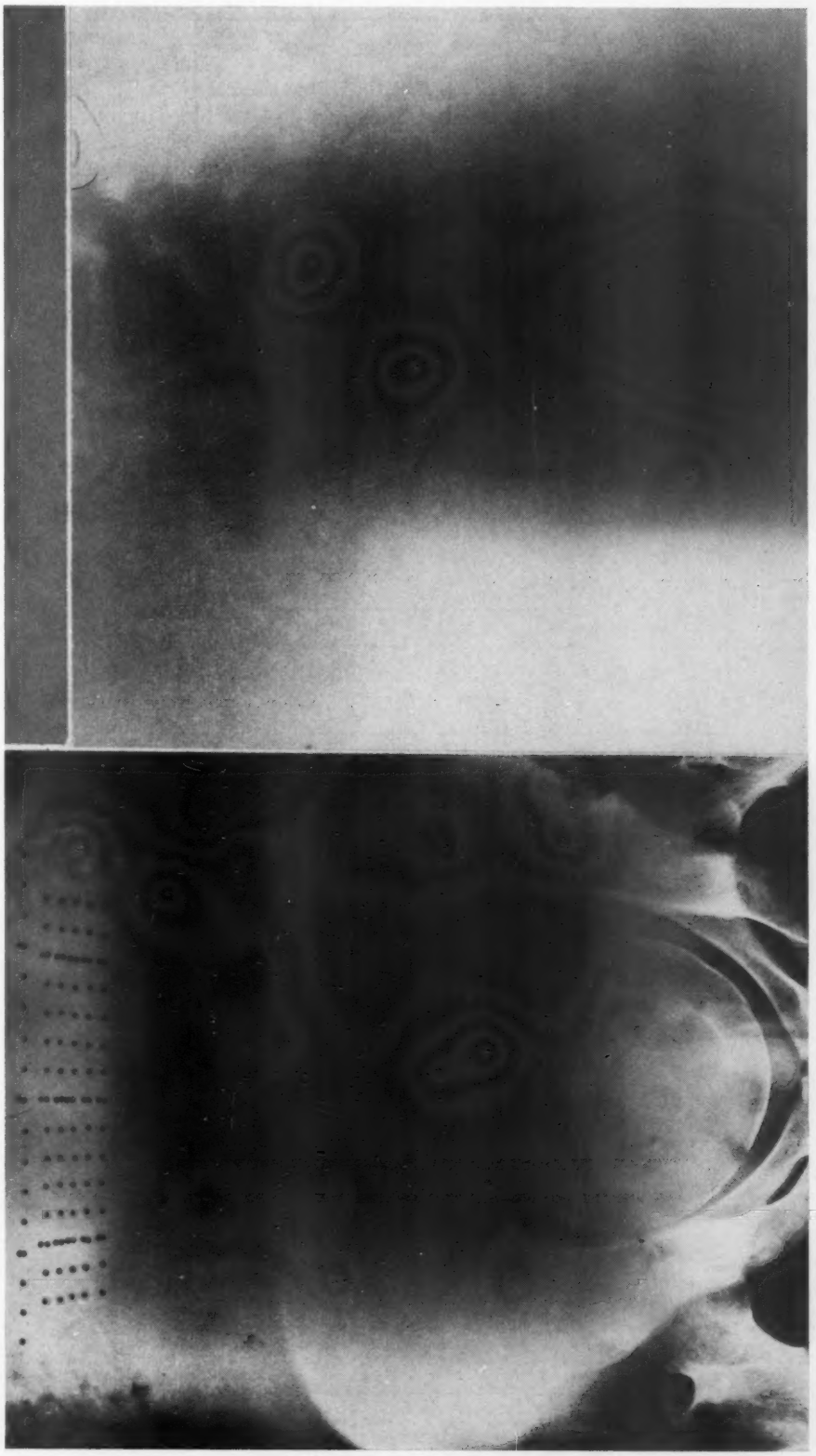

Fig. 2.—Subsequent revision of the films shown in Fig. 1. Revision was completed by the electronic scanning printer device. Details of the inlet and midplane are now satisfactorily visualized.

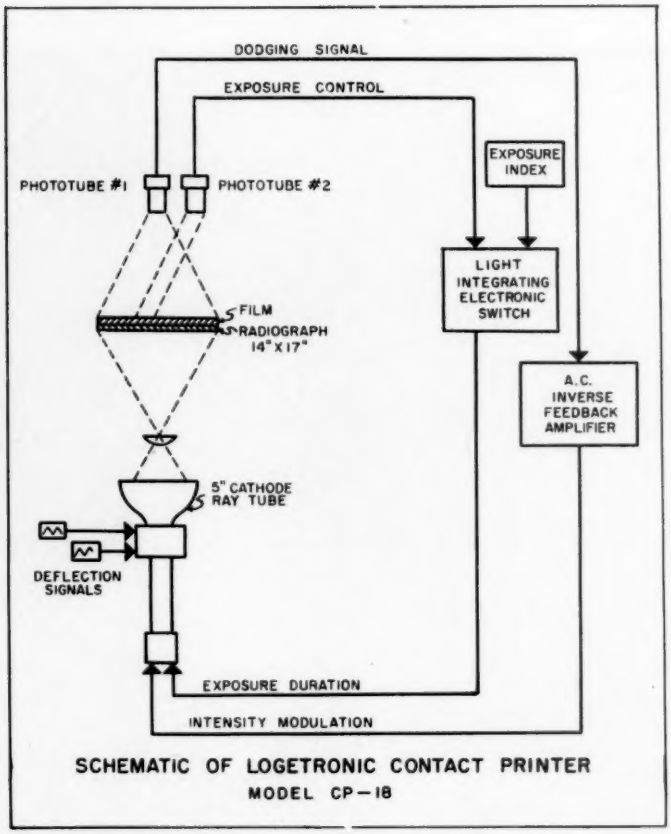

Fig. 3.—Schematic diagram of the geometry and circuits used in a LogEtronic contact printer.

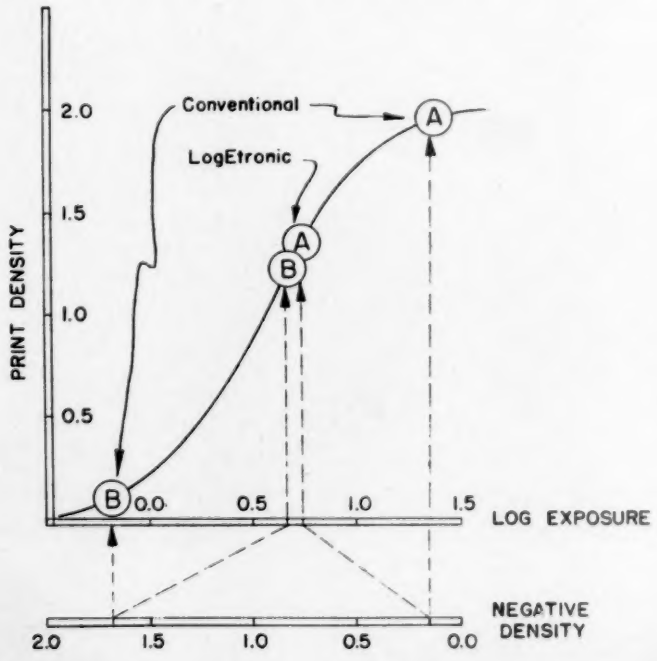

Fig. 4.—*For legend see opposite page.*

abdomen and pelvis. While a wedge filter was first used to improve diagnostic soft-tissue detail, it also served to reduce radiation exposure to the maternal and fetal soft parts.

2. Reduction of exposure by the advantageous use of high-speed screen combinations will reduce the required milliampere-seconds by 60 per cent, reducing the exposure dose by the same amount.

3. Further reduction of the exposure dose can be obtained by the use of a high-kilovoltage technique.

4. The recent developments of films with higher speeds have resulted in film techniques that permit reduction in the exposure dose by a factor of 50 per cent.

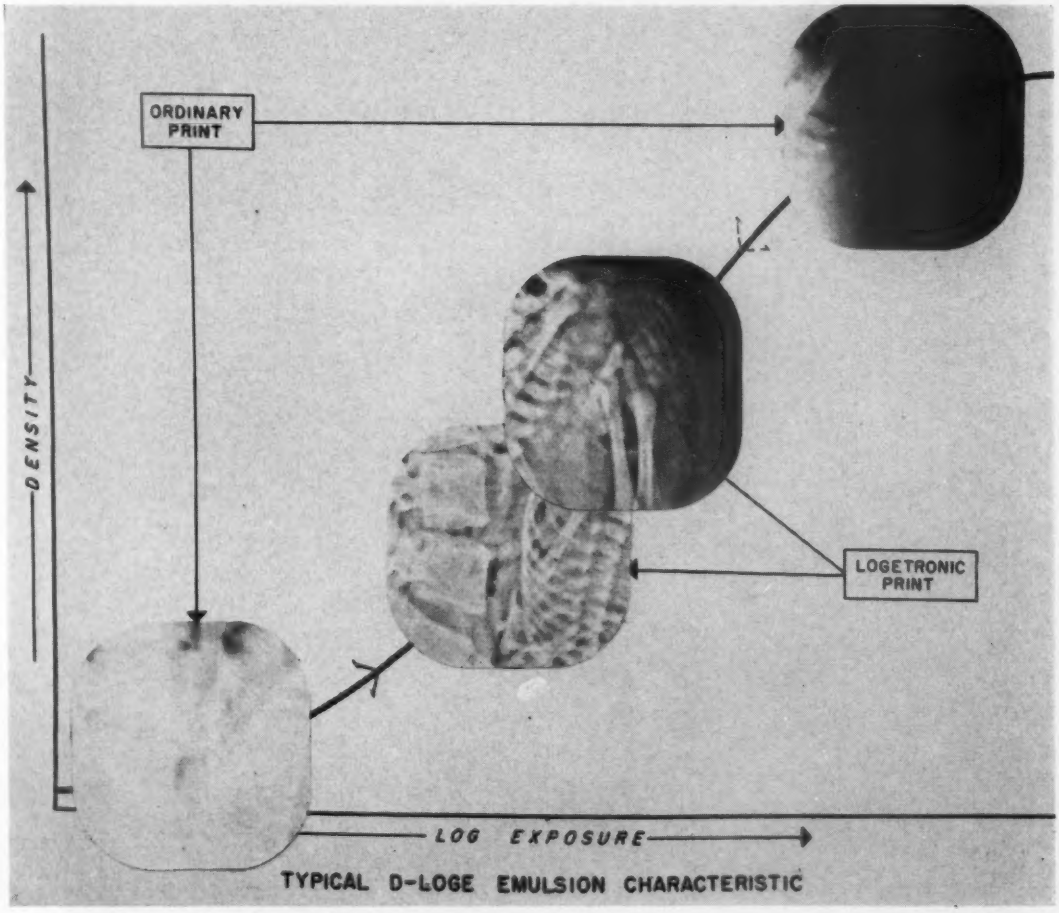

Fig. 5.—This demonstrates the ability of the LogEtronic printer to enhance detail. The lower left section (underexposed) and the upper right section (overexposed) were both taken from an ordinary print of a roentgenogram, i.e., placentagram. The two center sections, taken from a LogEgram made from the same roentgenogram, show a reduction in contrast between the sections plus greater detail contrast within the sections.

Fig. 4.—The D-LogE characteristic curve. Areas ordinarily exposed on the toe and shoulder of the curve are exposed by means of the LogEtronic electronic scanning device at mid-scale for maximum detail contrast and tone range. This demonstrates the response of a typical photographic emulsion to light. The high light and shadow regions (*A* and *B*), respectively, in the illustration and a negative would normally be printed at opposite extremes of the density scale where the slope of the curve is flat (local low contrast), and detail would, therefore, merge with its background. These two regions (*A* and *B*), however, in a LogEtronic print are reproduced near the middle of the scale where the curve is steep (high local contrast, resulting in better visual separation of diagnostic detail).

More precisely, the milliampere-second factor required to produce radiographs with similar diagnostic qualities is 50 per cent of that previously used when films with slower speeds were utilized. The kilovoltage factors used are the same and are not altered.

5. The use of the processing chemicals further to enhance and reduce exposure techniques is also important.

Fig. 6A.—This demonstrates an overexposed study of the uterus and fetus. The detail of the placental implantation is poor in the roentgenogram. The detail of the fetus is lost because of underexposure.

Method

The purpose of this project was the investigation of an electronic printing device as a method of reducing necessary radiation exposure. An empirical approach was used. The minimum film exposure factors for the pelvimetric

study were calculated. In these calculations use was made of high kilovoltage, increased aluminum filtrations, the recently developed fast film, high-speed screens, and the intensified developing techniques recommended by Whitehouse, Simons, and Evans.[6] The milliampere-second factor derived from these calculations was deliberately reduced 50 to 60 per cent. The film studies were completed with the use of this deliberate underexposure technique. The films

Fig. 6*B*.—The same film following electronic revision and printing shows the placenta on the anterior uterine wall.

were then processed and dried (Fig. 1). From these underexposed films, revised and corrected films of diagnostic quality were obtained by using an automatic scanning printer (Fig. 2).

The automatic scanning device is a photographic printer which uses electronic controls to produce diagnostic films from a wide range of under- or overexposed films.[3, 4]

The details of the principles utilized in the electronic scanning printer are embodied in the accompanying diagram (Fig. 3). A single cathode-ray tube is used as the printing source. A pair of stationary phototubes measures the diffused light penetrating the combination of radiographs and printing material. There are two independent circuits by which the phototubes control (1) the intensity of the light scanning source and (2) the duration of the exposure.

The cathode-ray tube is similar in construction to that used in laboratory oscilloscopes and acts as the scanning light source. This tube forms a spot of light on a short persistence fluoroscopic screen when bombarded by an electron beam. Light from this scanning spot is projected through the radiograph to expose the printing paper or film. Signals from the phototubes are used to modulate the intensity of the electron beam and can thus vary the light output of the cathode-ray tube. The circuits are so devised as to produce an inverse reaction. Thus, when a dense area in the radiograph is encountered, the scanning spot becomes brighter. When more translucent areas are encountered the scanning light source becomes correspondingly fainter. This produces a relatively uniform distribution of light over the printing area giving an evenly exposed print regardless of the wide variations of density in the original radiograph. The scanning light beam moves at a uniform velocity within the area being printed and since the beam overlaps it yields an exposure without evidence of scanning lines.

Results

The photographic effect of this method of film revision results in a simultaneous decrease and increase of contrast. While local contrast increases, the over-all contrast decreases. The effect of the apparatus is to produce a relatively uniform distribution of light at the photosensitive surface of the printing medium, which in turn produces a more uniformly exposed or dodged print (Fig. 4).

The final print of the pelvimetric study is made from the underexposed film. The preparation of an intermediate transparency permits numerous variations in the final step in terms of scale and printing material (Fig. 5).

Table I compares the radiation exposure (as measured in a pressed wood phantom) delivered to the maternal and fetal gonads during pelvimetric examination under three circumstances:

1. The use of conventional film, screens, and filtration.
2. The use of fast film, fast screens, improved filtration, and chemical development.
3. The use of deliberate underexposure with subsequent revision by automatic compensating electronic devices superimposed on the factors outlined in the preceding paragraph.

On the anteroposterior film of the pregnant abdomen the use of deliberate film underexposure techniques provided radiation exposure to the maternal ovaries and fetal gonads that was 60 per cent less than that provided by the fast film, fast screen, improved filtration and development technique alone.

The use of deliberate underexposure on the lateral pelvimetry films allowed a reduction of 40 per cent in the dose to the maternal ovaries and fetal gonads, as compared with the use of only fast screens and film.

Comment

Surely the electronic scanning devices are mechanisms to be utilized when unsatisfactory exposures have been completed and re-examination of the maternal pelvis is considered necessary. The radiation exposure which is occasionally

necessary during such re-examinations is thus obviated. Electronic revision of such films eliminates the additional radiation exposure dose. The mechanism of film revision has specific advantages in the reduction of radiation exposure. Its disadvantages are: (1) the delay necessary in the film processing, (2) the necessity for increasing the number of procedures in order to obtain a diagnostic film, and (3) the increased cost of the filming procedure. In our own minds this technique represents one of many mechanisms which must be investigated to produce diagnostic films with reduced radiation dose exposures. There are other electronic devices which are being investigated to improve the viewing of films. These devices utilize photographic electronic circuits such as are employed in television scanning procedures.

Summary

The routine use of an electronic photographic technique as a method for further reduction of radiation in obstetrical radiography is presented. Significant reduction in the calculated doses to the maternal ovaries and fetal gonads can be obtained in addition to the reduction in dose rate afforded by the use of high-speed screens, improved filtration, and improved developing techniques, with careful positioning of the patient.

We are especially indebted to Dr. Lee Buxton, Chairman of the Department and Professor of Obstetrics and Gynecology, Yale University.

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References

1. Clayton, C. G., Farmer, F. T., and Warrick, C. K.: Brit. J. Radiol. 30: 291, 1957.
2. Craig, Dwin R.: Photogrammetric Engineering 21: 556, 1955.
3. Craig, Dwin R.: M. & Biol. Illus., p. 166, 1957.
4. St. John, Elmer G., and Craig, Dwin: Am. J. Roentgenol. 78: 124, 1957.
5. Stewart, A., et al.: Lancet 2: 447, 1956.
6. Whitehouse, W. M., Simons, C. S., and Evans, T. N.: Am. J. Roentgenol. 80: 690, 1958.

X-RAY PELVIMETRY

EDWARD A. GRABER, M.D., HUGH R. K. BARBER, M.D., AND JAMES J. O'ROURKE, M.D., NEW YORK, N. Y.

(From the Obstetrical Services of Lenox Hill Hospital and St. Clare's Hospital)

SINCE the first x-ray pelvimetry in 1900, physicians have dreamed of making the delivery of a baby a mathematical problem that could be calculated with precision and certainty. This theory was and is most attractive, but the very fact that over two hundred different methods of x-ray pelvimetry have been advanced in the past 58 years refutes the idea that this goal has been attained. According to its advocates, modern radiological pelvimetry has almost achieved the ultimate in accuracy and usefulness. The purpose of this paper is to scrutinize the validity of this belief.

Since practically all pelvimetric x-ray examinations in New York City are interpreted and reported by radiologists, it was decided that the best way to arrive at a true and unbiased conclusion was to get pelvimetry reports from as many different radiologists as was practical. This gives one a broader base and a clearer average upon which to judge the results. Accordingly, private patients were sent to eighteen x-ray specialists in the greater New York area. The only prerequisite was that he be a member of the American Board of Radiology or be eligible for membership. In most instances, the patient was permitted to pick the doctor herself. Some of the physicians were in private practice, some were on the full time radiology staffs of hospitals in this area.

Most correlative surveys of clinical and x-ray studies of the pelvis are reported from large services with many obstetricians with different points of view controlling the delivery of the patients. It appears that, in order to be significant, the number of physicians participating should be as small as possible. Also, it seems desirable that they work together as a team and be similarly oriented on basic obstetrical principles. The cases reported in this series are those of our private patients whose delivery we controlled completely. Although the size of the group may be less impressive than others reported previously, we believe that the results are more uniform and perhaps of more consequence.

This report is based upon 242 pelvimetries and deliveries. Roughly, this represents about 15 per cent of the total number of deliveries. The methods of roentgen evaluation utilized were those of Thoms, Ball, Snow, Colcher and Sussman, and Caldwell and Moloy. These are the popular techniques of this community. They were all about equal in accuracy. It is concluded that the method used is not as important as the man using it.[1] We are not partial to any one.

The indications for x-ray pelvimetry in this series were rather loose. The intention was to get as wide a sampling as possible of normal and abnormal pelves. Some were taken about one week from term and some were taken when the patient was in labor. The indications are listed in Table I.

TABLE I

INDICATION FOR PELVIMETRY	NO. OF CASES
Unengaged head in primipara	74
Breech presentation	30
Brow presentation	2
Transverse presentation	1
Face presentation	1
Prolonged sterility	8
Previous myomectomy	5
Previous difficult delivery	18
Clinically questionable pelvis	28
Elderly primipara	15
Multiple pregnancy	10
Request by patient or referring physician	23
Dystocia	27
Total	242

The results in so far as the type of delivery is concerned are listed in Table II. Inasmuch as many prophylactic low forceps were done, low forceps and spontaneous deliveries are combined in the same column. The midforceps reported are all low midforceps. In cases requiring difficult high midforceps cesarean section was used.

TABLE II

INDICATION FOR PELVIMETRY	SPONTANEOUS OR LOW FORCEPS	LOW MIDFORCEPS	CESAREAN SECTION	TOTAL
Unengaged head in primipara	57	10	7	74
Breech presentation	27	0	3	30
Brow presentation	1	0	1	2
Transverse presentation	0	0	1	1
Face presentation	1	0	0	1
Prolonged sterility	8	0	0	8
Previous myomectomy	4	0	1	5
Previous difficulty	15	2	1	18
Questionable pelvis	13	5	10	28
Elderly primipara	12	1	2	15
Multiple pregnancy	9	1	0	10
Request	21	2	0	23
Dystocia	17	3	7	27
Total	185 (77%)	24 (9%)	33 (14%)	242

The section rate in this group was approximately 14 per cent. This represents a rate of roughly 2 per cent of our total deliveries. Our primary section rate runs about 3.6 per cent but of course other cesarean sections are done without previous pelvimetries as in antepartum hemorrhage, etc.

The next logical step was to determine the accuracy of the reports based on the prognosis submitted by the radiologist. This prognosis was almost universally given. It ranged anywhere from mentioning the mechanism of delivery to whether or not forceps would be necessary, whether molding was necessary, the level of arrest, or whether section was desirable. The accuracy is shown in Table III.

TABLE III

Correct on basis of clinical result	189	(78%)
Incorrect on basis of clinical result	53	(22%)
Total reports	242	(100%)

On the basis of these figures, the x-ray prognosis was inaccurate in about one out of 4 cases. On the surface, this indicates a reasonable predictive value, but this is not true on further analysis. The only reason for the respectable average of 78 per cent was that the vast majority of the reports dealt with a normal or almost normal pelvis and an average-sized baby. On further breakdown of these figures, it is seen that it is in the borderline situation that pelvimetry has its highest incidence of error. This group is summarized in Table IV.

TABLE IV. CASES IN WHICH PROGNOSIS WAS INCORRECT

1. Pelvis judged adequate, but clinically cephalopelvic disproportion due to larger baby than anticipated	16
2. Pelvis judged adequate, but clinically difficult delivery because of malpresentation, inertia, etc.	10
3. Pelvis judged borderline, but baby could be delivered by molding; clinically the patient could not be delivered vaginally	10
4. Pelvis judged borderline with delivery probably ending by cesarean, but clinically patient was delivered vaginally	5
5. Pelvis judged inadequate for delivery per vaginam, but clinically patient was delivered vaginally	2
6. Miscellaneous miscalculations	11
Total	54

Table V indicates the erroneous prognosis cases grouped on the basis of the original indication for x-ray pelvimetry. The results are self-explanatory. The highest percentage of error occurred when the obstetrician needed help the most.

TABLE V. ERRONEOUS X-RAY PROGNOSIS GROUPED BY INDICATION

INDICATION FOR PELVIMETRY	NO. OF CASES	NO. OF ERRORS	% ERRORS
Unengaged head in primipara	74	14	18.9
Breech presentation	30	5	16.6
Brow presentation	2	1	50
Transverse presentation	2	0	0
Face presentation	1	0	0
Prolonged sterility	8	0	0
Previous myomectomy	5	0	0
Previous difficult delivery	18	5	27.7
Questionable pelvis	22	11	50
Elderly primipara	15	1	6.6
Multiple pregnancy	10	0	0
Request	23	2	8.7
Dystocia	27	15	55.5

The crux of the whole problem of x-ray pelvimetry is in the incorrect prognosis group. It should be noted that the greatest percentage of error results from the inability of the roentgenologist to judge the size of the fetal head, regardless of the method used. He is able to measure the pelvis adequately, but must assume that the head is of average size. This is the major defect of pelvimetry. Thus, in the borderline pelvis group, the x-ray offers no real help. The same pertains to the cephalopelvic disproportion cases with an adequate pelvis, but a larger baby than normal.[2, 3]

There are many components to the mechanism of delivery. The radiologist is able to observe only two of these, the bones of the pelvis and the skull of the fetus. The point needing re-emphasis is, if the head cannot be measured with any degree of accuracy, how can the x-ray report give a prognosis as to the outcome of any specific delivery? Furthermore, unless a physician has an intimate knowledge of the clinical mechanisms of the various presentations and positions, the patient's parity and age, the condition of her soft tissues, her emotional stability, the strength and character of her uterine contractions, and, finally, sees the condition of the patient during labor—her hydration, fatigue, sedation, etc.—how can one in good conscience write down a prognosis?[4, 5] Yet, in this series, almost all the reports had an unsolicited prediction in the last sentence or two.

The radiologist is not at fault. He should not be criticized. He is merely trying to help the insecure obstetrician who asks his opinion as to whether the baby can or cannot be delivered vaginally. The x-ray report without a prognosis would be considered inadequate by many physicians.

The obstetrician has, however, produced a medicolegal Frankenstein by this practice. What defense can he have in court if he elects to deliver a baby vaginally in the face of a doubtful x-ray report, and the mother or child has a complication, even one that is not a result of disproportion? It would be very difficult to convince a lay jury that something as tangible as an x-ray picture is incorrect. From the moment an x-ray report with a prediction is on the chart, the obstetrician tends to lose control of his case.

What seems to have been forgotten is that x-ray pelvimetry is a laboratory adjunct to the physician's clinical judgment. It should be to the obstetrician what the white-cell count is to the surgeon treating appendicitis. If it helps the clinical picture, it is accepted. If not, it is discarded. The laboratory does not give a diagnosis or a prognosis when the blood count is submitted. It is not expected. In fact, it would be resented by a competent surgeon. Why, then, does an obstetrician expect or request a prognosis from the roentgenologist? It is our contention that the radiologist should report what he sees on x-ray pelvimetry. A report of this type will help the obstetrician in marshaling his facts for final judgment of a particular situation. It is strongly suggested that in the future the prognosis of the radiologist no longer be a part of his evaluation.

The obstetrician should not be intimidated by the x-ray. An adequate trial of labor is still the best way of testing pelvic capacity. A closely observed labor rarely hurts a mother or child. As long as progress is satisfactory, one is safe.[6] When progress ceases, a prompt decision should be made regarding delivery from above or below. The most valuable measurement in obstetrics is the fetal yardstick.[7] There is no better measurement of pelvic capacity than a head on the perineum. Any contracted plane reported on an x-ray film is merely relative.[8] There may be compensatory room in front or back, the head may mold, the contractions may force the head through, the head may be smaller than anticipated, etc. Unless there is superimposed uterine inertia, one should generally give nature a chance.

X-ray pelvimetry is of little value in solving most obstetric problems.[9] There is still no substitute for an adequate vaginal examination in labor, when the size of the head can actually be judged in relation to the size of the pelvis. No laboratory aid can take the place of clinical experience.

It is our belief that the indications for x-ray pelvimetry are too broad and should be changed. The usual list includes: (1) floating head in a primipara at term, (2) breech presentation, (3) elderly primiparity, (4) malpresentations,

(5) previous difficult delivery, (6) lack of satisfactory clinical progress, (7) clinically abnormal pelvis, (8) cephalopelvic disproportion, (9) any condition, such as sterility, with a high priority baby.

Pelvimetry can be diminished by about 70 per cent if the indications are reduced to two: (1) malpresentation, and (2) lack of satisfactory progress in labor.

In these situations, x-ray will aid in the final evaluation of the situation and in determining the most appropriate method of delivery. All other indications listed can best be handled by time, physical examination, and by clinical experience. The potential harm of x-ray pelvimetry may still be questionable, but in most cases it is certainly unnecessary to expose mother and child.

X-ray pelvimetry is of greatest value during labor. If the plates are taken before the onset of labor, conditions may change radically by the time labor ensues. Labor pushes the head into the pelvis or at least into the brim where it can be roughly compared in size with that of the pelvic cavity. It is impossible to obtain even a rough indication if the head is floating. Also, the actual mechanism of labor can be determined after a few hours of labor, and this information may be helpful.

During the past 3 years we have become more conscious of the effect of radiation on both mother and child. The average x-ray pelvimetry exposes the gonads of each to about 0.7 r, the total body dose being 3.5 to 4.5 r.[10, 11]

There is little doubt that x-ray in any dosage causes gene mutations, and many of these are deleterious. The permanently altered genes will be duplicated in the offspring in all the future generations. Since the amount of mutation depends on the cumulative dose of radiation, it behooves us in these days of atomic bomb tests to keep all unnecessary medical radiation at a minimum.

According to Glass,[12] there are 80,000 births annually in the United States of genetic defectives due to natural mutations. It is estimated that the additional radiation the present generation is exposed to will increase this by 10 per cent.

British studies on the genetic effects of radiation are quite disturbing.[13] One states that cancer is increased by 80 per cent in adults who were radiated with diagnostic dosage in utero. Another indicates that the leukemia rate of children radiated in utero is twice that of the general population. Further studies to confirm or deny these reports are necessary before they can be taken seriously, but certainly, in the face of this present evidence, unnecessary pelvimetry should be discouraged.

In indicated cases, one should not hesitate to take the necessary films. It should be noted that the term "necessary films" is used. The fewer the plates taken, the less the number of roentgens delivered.

It seems wrong for any service to adhere to a fixed routine method of pelvimetry. It is incongruous routinely to take five views as a matter of course, if they are not indicated. The greatest exposure occurs with the inlet view. If the head is in the inlet and one is looking for a midplane contraction, certainly an anteroposterior and a lateral view are all that are indicated. The outlet can be measured manually, and we are in agreement with Parlee[14] that outlet plates should be eliminated. In short, the fewer the plates, and the faster the film, the safer the x-ray. The obstetrician should state exactly how many and which films he wants. There should be no routine.

The status of x-ray pelvimetry has been reviewed. It is hoped that with the newer emphasis on the dangers of radiation and with the many limitations of pelvimetry again emphasized, radiological estimation of pelvic capacity will lose some of its undeserved present-day popularity, and will again assume its indicated role, that of a laboratory aid.

Summary

1. Two hundred and forty-two cases of x-ray pelvimetry reported by eighteen different radiologists are reviewed on the basis of the prognostic accuracy of the reporting physician.

2. Three out of four were reported correctly, but almost all of these were in the adequate pelvis with an average-sized baby.

3. The radiologist has no method of measuring the fetal head adequately, and was in error most frequently in the cases where the obstetrician needed help —the cases of cephalopelvic disproportion, due either to the borderline pelvis, or to the unsuspected larger baby in an average pelvis.

4. It is suggested that the roentgenologist does not usually have sufficient information or the obstetrical background to make a clinical prognosis and should cease predicting the outcome of delivery. Furthermore, by his predictions, he places the obstetrician in an untenable position medicolegally.

5. X-ray pelvimetry was never intended to take the place of an adequate pelvic examination in labor, and a trial of labor. It is a laboratory aid at best and should be used as such.

6. The indications for x-ray pelvimetry should be limited to two situations: (1) malpresentation, and (2) lack of adequate clinical progress in labor. Further, it is our opinion that x-rays should be taken only while the patient is in labor for maximum information.

7. Since all radiation is harmful, it is our belief that all routines as to the number of plates should be discarded. A specific minimum number of views should be ordered by the obstetrician for the individual case.

References

1. Lilienfeld, A. M., Treptow, E., and Dixon, D. M.: Human Biol. **21**: 143, 1949.
2. Williams, E. R., and Phillips, L. G.: J. Obst. & Gynaec. Brit. Emp. **53**: 125, 1946.
3. Kaltreider, D. F.: Am. J. Obst. & Gynec. **63**: 116, 1952.
4. Eastman, N. J.: Obst. & Gynec. Surv. **3**: 301, 1948.
5. Dyer, I.: Am. J. Obst. & Gynec. **60**: 302, 1950.
6. Brown, W. E.: South. M. J. **44**: 1046, 1951.
7. Weinberg, A.: Obst. & Gynec. Surv. **7**: 455, 1952.
8. Kaltreider, D. F.: Am. J. Obst. & Gynec. **63**: 392, 1952.
9. Haas, R. L., Latourette, H. B., and Whitehouse, W. M.: Surg. Gynec. & Obst. **99**: 462, 1954.
10. Eastman, N. J.: Obst. & Gynec. Surv. **12**: 315, 1957.
11. Berman, R., and Sonnenblick, B. P.: Am. J. Obst. & Gynec. **74**: 1, 1957.
12. Glass, B.: Am. J. Roentgenol. **78**: 955, 1955.
13. Duffy, B. J., Jr.: J. Clin. Endocrinol. **17**: 1383, 1957.
14. Parlee, S. S.: Am. J. Obst. & Gynec. **75**: 327, 1958.

PROLONGED LABOR*

HARRY FIELDS, M.D., JOHN W. GREENE, JR., M.D., AND ROBERT R. FRANKLIN, M.D., PHILADELPHIA, PA.

(From the Department of Obstetrics and Gynecology, School of Medicine, University of Pennsylvania)

"Wait to see what nature can effect, not what she can endure."
—Sir James Y. Simpson, 1871

IT IS generally accepted that the average duration of normal labor in the primiparous patient is about 14 hours and in multiparas about 8 hours.[3] Therefore, when the process of parturition is not completed in these times, it can be considered abnormal or a variation of normal. If this be so, labor lasting longer than these arbitrary limits should be considered as complicated, and thus may exert a deleterious effect on mother and infant. Obstetricians[1, 2, 4, 6, 7, 8] have recognized prolonged labor as a complication which results in dangerous sequelae such as maternal morbidity, postpartum hemorrhage, and fetal morbidity or mortality. Studies of prolonged labor reported in the literature have used different definitions of prolongation, from 18 hours in the multipara and 24 hours in the primigravida[4, 5, 9-12] to 30 or more hours[2, 6, 7] as the period of time after which labor should be considered prolonged.

Material and Methods

In an attempt to determine the deleterious effects on the mother and infant, a review of prolonged labor was conducted at the Hospital of the University of Pennsylvania. Material was obtained by reviewing all obstetrical charts from January, 1945, to December, 1954, inclusive. The statistics were analyzed to learn means of preventing prolonged labor and methods of managing it once it had developed. For the purpose of comparison, the material is divided into two 5 year periods, the first from 1945 through 1949 (Period I) and the second from 1950 through 1954 (Period II). The two periods are similar except that more deliveries occurred in the second period. All patients, ward and private, were under the care of the same attending obstetricians. For ward patients, the labors and deliveries were conducted by the residents under the direct supervision of these attending staff obstetricians.

Frequently it was impossible to determine the onset of labor. We used as our criterion the first regular, painful uterine contractions that eventuated in the birth of an infant. In this report, labor was considered prolonged when it lasted 24 hours or longer in a primipara and 18 hours or longer in a multipara.

*Presented at a meeting of the Obstetrical Society of Philadelphia, Oct. 3, 1957.

Incidence

During the 10 year period (1945-1954) there were 21,201 deliveries (Table I). Among these, there were 781 (3.7 per cent) cases which were considered prolonged labor by the above criteria. There were almost equal numbers of ward and private patients during this period. The incidence of prolonged labor, however, was 2.2 per cent among the private patients and 5.2 per cent among the ward patients. In Table II the material is divided into two 5 year periods, which are used as a basis for comparison.

TABLE I. INCIDENCE, 1945-1954

	NO. DELIVERIES	PROLONGED LABOR	
		NO.	%
Private	10,655	235	2.2
Ward	10,546	546	5.2
Total	21,201	781	3.7

TABLE II. COMPARATIVE INCIDENCE

	1945-1949			1950-1954		
	NO. DELIVERIES	PROLONGED LABOR		NO. DELIVERIES	PROLONGED LABOR	
		NO.	%		NO.	%
Private	4,082	149	3.7	6,573	86	1.3
Ward	4,684	280	6.0	5,862	266	4.5
Total	8,766	429	4.9	12,435	352	2.8

Length of Labor

Table III gives a breakdown of the length of labor. Thirty hours has been considered by some other authors[2, 6, 7] as the time limit after which labor should be considered prolonged. By use of this criterion, a large segment of the cases would be excluded from the study. The total number of cases in the first 5 year period would then be reduced from 429 to 198 (46 per cent) and in the second 5 year period from 352 to 76 (21.6 per cent).

TABLE III. LENGTH OF LABOR

HOURS	1945-1949			1950-1954		
	NO.		%	NO.		%
18-23	75		17.5	107		30.4
24-30	156		36.3	169		48.0
31-36	83		19.3	42		11.9
37-42	51		11.9	21		6.0
43-48	24	198	5.7	11	76	3.1
49-54	17		4.0	1		0.3
55 plus	23		5.3	1		0.3
Total	429		100.0	352		100.0

Type of Delivery

In a review of the types of delivery after prolonged labors, four aspects are of special interest (Table IV): (1) There has been an increase in the number of spontaneous deliveries in Period II. (2) The 20 per cent incidence of midforceps deliveries does not show a significant change in the two 5 year periods. Twenty per cent midforceps deliveries is almost twice the normal

incidence for the whole clinic. (3) The decrease in vaginal delivery of breeches in Period II was due to an increase in the incidence of cesarean section for breeches in prolonged labor; in Period I, cesarean section was performed in 5 of 24 cases of breech presentation, whereas in Period II, it was done in 5 of 8 breech presentations. (4) The cesarean section rate for prolonged labor for the 10 year period was 12.9 per cent, three times the primary cesarean section rate of the entire obstetrical service. Comparison of Period I and Period II, however, shows the cesarean section rate to have dropped from 17.0 to 7.9 per cent. During the same periods of time, the primary cesarean section rate for the clinic in general decreased from 5 per cent in Period I to 3.3 per cent in Period II.

TABLE IV. TYPE OF DELIVERY

DELIVERY	1945-1949		1950-1954	
	NO.	%	NO.	%
Spontaneous	137	31.9	149	42.3
Low forceps	110	25.9	98	27.8
Midforceps	86	20.1	68	19.3
High forceps	1	0.2	1	0.3
Dührssen's	1	0.2	2	0.6
Twin	2	0.5	3	0.9
Breech	19	4.4	3	0.9
Cesarean section	73	17.0	28	7.9
Total	429	100.0	352	100.0

Indications for Cesarean Section

Realizing the difficulty of selecting a single reason for performing a cesarean section, we attempted to pick the most cogent indication. This study showed the paramount etiological factor in prolonged labor to be uterine inertia (Table V). It was the primary indication in the first period for 45 of 73 cesarean sections, and in the second period, for 20 of 28 cesarean sections. The use of cesarean section for uterine inertia during prolonged labor decreased appreciably during the second 5 year period.

TABLE V. INDICATIONS FOR CESAREAN SECTION

INDICATION	1945-1949 429 CASES		1950-1954 352 CASES	
	NO.	%	NO.	%
Inertia	45	10.5	20	5.6
Cephalopelvic disproportion	20	4.7	1	0.3
Fetal distress	5	1.1	5	1.4
Constriction ring	0	0.0	1	0.3
Cervical dystocia	2	0.5	0	0.0
Cervical myoma	1	0.2	1	0.3
Total	73	17.0	28	7.9

Maternal Complications

There were no maternal deaths in the entire series. Although there has been a decrease in both the maternal morbidity and the incidence of postpartum hemorrhage, they are still considerably higher than those for the obstetrical service as a whole (Table VI).

TABLE VI. MATERNAL COMPLICATIONS

	1945-1949		1950-1954	
	% ENTIRE CLINIC	% PROLONGED LABOR	% ENTIRE CLINIC	% PROLONGED LABOR
Morbidity	5.1	14.5	1.2	10.0
Postpartum hemorrhage	4.2	11.7	1.8	6.2

Infant Mortality

Careful study of infant mortality in the cases of prolonged labor reveals a 3.3 per cent incidence of intrapartum and neonatal deaths in Period I and none in Period II (Table VII). In the former period, 2 babies died of congenital defects incompatible with life and one died intrapartally after 9 hours of labor, leaving 11 infants who succumbed to some condition which seemed to be related to prolonged labor. Antepartum deaths were not used in this calculation. In the remaining 11 fetal deaths, all of which occurred in Period I, there was a definite relationship between fetal mortality and length of labor (Table VIII).

TABLE VII. INFANT MORTALITY

WEIGHT (GRAMS)	1945-1949			1950-1954		
	ANTE	INTRA	POST	ANTE	INTRA	POST
1,000-2,499	2	3	1	1	0	0
2,500-3,999	2	4	5	1	0	0
4,000 or more	0	1	0	1	0	0
Total	4	8	6	3	0	0
		3.3% of prolonged labor cases			0.0% of prolonged labor cases	

TABLE VIII. INTRAPARTUM AND NEONATAL DEATHS, PERIOD I (1945-1949)

BABY NO.	LENGTH OF LABOR	TYPE OF DELIVERY	TIME OF DEATH	ETIOLOGY
1	18 hours	Spontaneous	Neonatal	Congenital heart abnormality
2	24 hours	Spontaneous	Intrapartum 24 hours	Renal agenesis
3	28 hours	Spontaneous	Neonatal	Respiratory difficulty
4	30 hours	Low forceps	Intrapartum 30 hours	Cerebral trauma
5	36 hours	Low forceps	Intrapartum 36 hours	Tentorial tear
6	40 hours	Low forceps	Intrapartum 9 hours	Undetermined
7	42 hours	Cesarean section. Indication, inertia	Neonatal	Pneumonia
8	44 hours	High forceps	Neonatal	Cerebral trauma, pneumonia
9	47 hours	Cesarean section. Indication, inertia	Intrapartum 27 hours	Postmaturity, 43 weeks. Autopsy negative
10	48 hours	Craniotomy Dührssen's incisions	Intrapartum 24 hours	Intrauterine infection
11	53 hours	Breech	Intrapartum 53 hours	Cerebral trauma
12	54 hours	Cesarean section. Indication, inertia	Neonatal	Pneumonia
13	57 hours	Breech	Neonatal	Tentorial tear
14	84 hours	Cesarean section. Indication, inertia	Intrapartum 50 hours	Postmaturity, 44 weeks. Intrauterine infection

Treatment

It is obvious that the second 5 year period shows a great improvement over the first, even though the type of patient studied was similar in each

group. When the various methods of treatment during prolonged labor were analyzed, a definite difference was discernible between the two periods (Table IX). "Analgesia, adequate" indicates that the patient received analgesia in some form (Demerol, morphine, Dilaudid) at least every 4 hours within 12 hours of delivery. "Analgesia, inadequate" indicates that the patient received no analgesia during her labor or that the interval was greater than 8 hours. In some of the records, information concerning analgesia was insufficient to make a decision as to adequacy or inadequacy. The figures indicate a definite improvement, however, in the general management of patients in labor with respect to rest and hydration. The use of Pitocin in the treatment of prolonged labor was increased in the second 5 year period, mainly because of the advent of the intravenous administration of Pitocin in dilute solution. The use of caudal anesthesia also increased in the second 5 year period from 8 (1.9 per cent) to 46 cases (13.1 per cent).

TABLE IX. TREATMENT DURING LABOR

TREATMENT	1945-1949		1950-1954	
	NO.	%	NO.	%
Analgesia, adequate	190	44.4	266	75.6
Analgesia, inadequate	184	43.0	54	15.3
Analgesia, status not determined	55	12.6	32	9.1
Intravenous fluids	33	7.6	73	26.4
Antibiotics	49	11.4	106	30.1
Amniotomy	119	27.7	78	28.4
Pitocin, intravenously	7	1.6	69	19.6
Pitocin, intramuscularly	62	14.5	58	16.5
Caudal	8	1.9	46	13.1

Comment

It is felt that the reduction in incidence and improvement in results in prolonged labor indicate better recognition of the problem and better management. This might have been accomplished by doing cesarean sections earlier. The figures may imply this at first glance. Careful scrutiny of the statistics for the entire obstetrical service, however, discloses that fewer primary cesarean sections were done for inertia in the 1950-1954 period than in the 1945-1949 period (Table X). Also, fewer primary cesarean sections were done in the second period for inertia in patients in whom labor did not become prolonged. This proves that the reduced incidence of prolonged labors in the second period was not accomplished by increasing the cesarean section rate on the obstetrical service. The over-all primary cesarean rate dropped from 5.0 per cent in the first period to 3.3 per cent in the second 5 year period. Cesarean section was not the answer to the reduction in the incidence of prolonged labor. Therefore, early recognition, treatment, and management during labor should be considered as the important factors that accomplished this improvement.

TABLE X. INDICATIONS FOR PRIMARY CESAREAN SECTION AT THE HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA

INDICATION	1945-1949		1950-1954	
	NO.	%	NO.	%
Cephalopelvic disproportion	102	23.2	100	24.1
Uterine inertia	82	18.5	50	12.5
Others	257	58.3	266	63.4
Total no. primary sections	441	100.0	416	100.0
Total no. deliveries	8,766		12,435	

It must be emphasized that, although cesarean section is not the answer to prolonged labor, it should be used when indicated, without unnecessary delay. Important decisions should be made early in labor when cephalopelvic disproportion is present or there is an abnormal presentation or insurmountable abnormality in the pelvis. If vaginal delivery cannot be anticipated without effects deleterious to the mother or infant, cesarean section should be decided upon promptly.

Adequate analgesia, more frequent use of intravenous fluids, antibiotics, intravenous Pitocin, and caudal anesthesia may be factors that have caused the marked reduction in incidence of prolonged labor and the improvement in results after its occurrence in the second 5 year period. It is apparent that uterine inertia is the outstanding etiological factor. It is therefore this aspect of labor that must be better understood and managed. The judicious use of amniotomy, intravenous Pitocin, and caudal analgesia has corrected uterine inertia and permitted vaginal delivery many times.

A word of caution must be interjected. To use these aggressive forms of therapy in the management of complications of labor requires thorough training, mature judgment, and constant personal observation. Amniotomy should be performed only by one experienced in the technique. The use of intravenous Pitocin has been the subject of much discussion in obstetrical circles in recent years. Some precautions should be emphasized. There should be no question of cephalopelvic disproportion. Constant attendance by an experienced person is essential whenever intravenous Pitocin is running. The rate of flow must constantly be adjusted depending upon the uterine response. Fetal heart sounds must be carefully followed throughout this procedure. Caudal analgesia should be used only by an experienced physician who can remain with the patient constantly.

The decision as to the appropriate time for instituting these methods of treatment can be made only by an experienced obstetrician who has kept pace with current obstetrical progress.

Fear of "meddlesome obstetrics" can be discarded if sound obstetrical judgment and experience replace the laissez-faire attitude present in many areas of obstetrical practice. The old attitude toward "sedation and fluids" as the only treatment in labor should be replaced by a more progressive approach to treatment. Patients in labor must receive more constant and concentrated care instead of casual intermittent observation based on the premise that, if given enough time, nature will see to it that the baby is successfully born. Reid[8] has aptly stated, "Unfortunately, watchful expectancy is not always associated with brilliant results in these cases of prolonged labor resulting from uterine inertia."

Summary

1. A 10 year study of labor lasting 24 hours or longer in the primipara and 18 hours or longer in the multipara has been carried out at the Hospital of the University of Pennsylvania.

2. The statistics were divided by 5 year periods, the first from 1945 through 1949 and the second from 1950 through 1954. During the first 5 years there were 8,766 deliveries with 428 (4.9 per cent) instances of prolonged labor, and during the second 5 years there were 12,435 deliveries with 352 (2.8 per cent) instances of prolonged labor.

3. There was a marked reduction in the length of labor in the second 5 year period. Only 76 of 352 labors during the second period lasted longer

than 30 hours, while in the first 5 years, 198 of 429 prolonged labors lasted longer than 30 hours.

4. The maternal morbidity rate was 14.5 per cent for the first period and 10.0 per cent for the second. The incidence of postpartum hemorrhage in prolonged labor was 11.7 per cent in the first 5 years and 6.2 per cent in the second period.

5. In the first 5 year period 11 infants (2.6 per cent) died of causes which seemed to be related to prolonged labor. No intrapartum or neonatal deaths occurred in the second 5 year period.

6. Analysis of methods of treatment showed that during the second 5 year period more patients received "adequate analgesia," intravenous fluids, antibiotics, intravenous Pitocin, and caudal anesthesia.

Conclusions

Factors responsible for better results in prolonged labor include better general obstetrical care, closer supervision and observation of patients during labor, with better sedation and hydration, and the judicious use of antibiotics, intravenous Pitocin, and caudal anesthesia.

Better obstetrical results will be obtained with a more aggressive program of management and care during labor, rather than one of intermittent watchful expectancy.

References

1. Corner, G. W., Jr., Kistner, R. W., and Wall, R. L.: Am. J. Obst. & Gynec. 62: 1086, 1951.
2. Douglas, R. G., and Stander, H. J.: Am. J. Obst. & Gynec. 46: 1, 1943.
3. Eastman, N. J.: Williams Obstetrics, ed. 11, New York, 1956, Appleton-Century-Crofts, Inc.
4. Evans, T. N.: Obst. & Gynec. 6: 522, 1955.
5. Huber, C. P.: Postgrad. Med. 15: 383, 1954.
6. Keettel, W. C., and Pettis, G. S.: Obst. & Gynec. 7: 15, 1956.
7. McCain, J. R., Anderson, C. L., Lester, W. M., and Pilkington, J. W.: J. A. M. A. 153: 695, 1954.
8. Reid, D. E.: Am. J. Obst. & Gynec. 52: 719, 1946.
9. Schmitz, H. E., Bremner, J. X., Towne, J. E., and Baba, G. A.: Am. J. Obst. & Gynec. 54: 643, 1947.
10. Starr, S. H.: Am. J. Obst. & Gynec. 63: 333, 1952.
11. Williams, P. F.: J. Michigan M. Soc. 42: 365, 1943.
12. Willson, J. R., and Alesbury, R. J.: Am. J. Obst. & Gynec. 61: 1253, 1951.

WILLIAM SMELLIE AND THE MECHANISM OF LABOR

HARRY OXORN, M.D., F.R.C.S. (C.), MONTREAL, QUEBEC

(From the Department of Obstetrics and Gynaecology, Royal Victoria Hospital, and McGill University)

IT IS an enigma of history that a man's name is not always associated with, or remembered for, his best work. William Smellie is a good case in point. Mention of his name brings to mind the Mauriceau-Smellie-Veit maneuver for delivery of the aftercoming head. In the first place, while Smellie may have figured out this procedure independently, most historians acknowledge Mauriceau's claim to priority. In the second place, this maneuver, useful as it may be, is of minor importance when compared with his many far greater contributions to obstetrics.

William Smellie, the Master of British Midwifery, was born in Scotland in the township of Lanark in 1697, and died there in 1763 at the age of 66. He spent all but 20 years of his life in Lanark.

Life of Smellie

Boyhood and Education.—Our knowledge of Smellie's boyhood, his early education, and his medical training is not accurate. While Smellie was born into, and practiced in, a Scotland which was in a state of direst poverty, his parents were in comfortable circumstances. He was probably an only child, and received his education at the grammar school in Lanark. He studied music and art, and his likeness which hangs in the Royal College of Physicians in Edinburgh is believed to be a self-portrait. He married Eupham Borland in 1724 when he was 27, and while the union was a happy one, the couple had no children.

His medical training, by apprenticeship, was probably attained in Glasgow under Dr. John Gordon. This prominent physician later trained Tobias Smollett, who became a famous novelist. Smellie began practice in 1720 without a medical degree. In 1733 he became a member of the Faculty of Physicians and Surgeons of Glasgow. In 1745 he received the degree of M.D. of the University of Glasgow.

He began his career in Lanark in 1720 at the age of 23, and remained for 19 years. He left in 1739 to settle in London. In 1759 he retired to his birthplace where he worked on his book until his death in 1763.

Early Practice.—In Lanark Smellie practiced general medicine including surgery. There is a bill extant dated 1723 for the amputation of a leg. He was interested in midwifery and made careful notes on his unusual cases. His reputation grew rapidly, and he was called in consultation by both the local midwives and those in surrounding towns. Smellie must have been physically fit, for most of his journeys to neighboring villages were on foot or on horseback over rough roads. In his early years he had no forceps, and he wrote that

when the head was high he could deliver by version and extraction, but that when the head was impacted low in the pelvis he was forced to perform a destructive operation on the child.

Move to London.—While he carried on his general practice his experience in obstetrics grew steadily. In 1739 he left Lanark. The reason for this move is not known. He was likely dissatisfied with some aspect of his obstetrical knowledge or ability. He went first to London to attend lectures on midwifery, and thence to Paris to see the Gregoires, father and son. He was impressed in neither city. Feeling, probably, that he knew as much as and could teach as well as the men he met, he returned to London and settled there in 1740 for the purpose of practicing and teaching midwifery.

The living conditions in London were dreadful. Housing was deplorable. Families lived in a single room often without a window, to avoid paying the window tax. Personal hygiene and standards of cleanliness were on a low level in all classes. Among the poor only one child out of four survived its fifth year. The exposure on the streets of unwanted children and even deliberate infanticide were commonplace.

Obstetrics was controlled by the midwives. No formal training was required, and any woman could set herself up in practice. Licensing was in the hands of the bishops, who based their decisions on moral grounds rather than on skill and knowledge. Many of these women knew little and cared less. Smellie campaigned for the training and examination of midwives, and their supervision by competent medical personnel. At the same time he fought for the status of the doctor as obstetrician. He recognized the need for efficient maternity services, and largely as a result of his efforts, several lying-in hospitals were opened in London. For unknown reasons he never attained a position on the staff of any of these institutions.

Smellie worked in London for 20 years. Having neither social graces nor social ambitions, he did not attract the aristocratic clientele of his pupil and rival, William Hunter. Smellie's skill, sagacity, and humanity were evident in the lying-in room, and he described his private practice as being "pretty extensive." While he could be frank and outspoken when the occasion demanded it, as a rule he did not speak easily with people. He had, however, many friends of first rank.

Teacher of Obstetrics.—He began teaching in 1741, giving private courses for which the students paid. A course of instruction lasted two weeks. Two hours each day were given over to lectures on theory and practice. Smellie was mechanically minded and constructed ingenious models of the fetus and the human pelvis. On these machines he demonstrated the various presentations of the fetus, and the course and management of labor in normal and abnormal cases. Smellie realized that this was not enough, that adequate instruction could not be achieved without clinical demonstrations on living patients. Copying the method of Gregoire in Paris, he let it be known that he, with his students, would attend the confinements of poor women in their own homes, free of charge. Each student paid 6 shillings into a common fund to assist the especially needy patients.

Smellie was one of the earliest teachers of midwifery in Great Britain, and he surpassed by far the few men who preceded him. During 10 years he gave 280 courses to more than 900 students from all parts of the world. In that series over 1,100 women were delivered free of charge.

Smellie was attacked by three groups of people. (1) Because he was the chief exponent of man midwifery he was the subject of scurrilous pamphlets by the midwives. Constant reference was made to his large hands and the indecency of men doing vaginal examinations. (2) Because he was the best

teacher of his time he aroused the envy of lesser men. (3) Because he thought for himself, investigated for himself, and refused to accept what had been handed down from the time of Hippocrates, he aroused the bitter antagonism of the supporters of the traditional teaching. One of his most violent attackers was a prominent obstetrician, John Burton, who became the model for Doctor Slop in Sterne's novel, *Tristram Shandy*. Other attackers included William Douglas, Philip Thicknesse, and Mrs. Elizabeth Nihell, the leading midwife of her day. Smellie shunned publicity and scarcely deigned to answer his critics. He did not let these attackers deter him, nor did they arrest the success of his school of instruction, for pupils came from all parts of the world.

Obstetrical Contributions

Normal Mechanism of Labor.—Had William Smellie done nothing else, his description of the passage of the fetal head through the maternal pelvis would have won him a place in history. His work on the mechanics of labor is the basis of scientific midwifery, one of the great contributions to obstetrics.

Before Smellie's original work, most of the doctrines were passed down from the ancients, author to author, without any new observations being made. Smellie was one of a very few men who, because they attempted to replace tradition by personal observation, were attacked as heretics. So it was with the mechanism of parturition. The current belief was that the baby entered the pelvis in the anteroposterior diameter, occiput toward the symphysis and face to the sacrum, and passed through the pelvis by virtue of its own efforts aided by the propulsive force of the uterus. It was as though, with the woman lying on her back, the baby crawled into the world on its hand and knees. There was no suspicion that there was any complexity in the process, and hence no understanding of difficult cases.

The only writer before Smellie to challenge tradition was Fielding Ould. He noted: "The breast of the child does certainly lie on the sacrum of the mother, but the face does not; for it always (when naturally presented) is turned to one side or the other, so as to have the chin directly on one of the shoulders." Ould reasoned that the longest diameter of the head and of the shoulders should enter the largest diameter of the inlet, which he believed to be the transverse. He did not see that the head could not continue in the pelvis in the transverse, but had to turn, which suggests that he did not make a careful study of the whole pelvis. He detracted from his original and important observation by stating that the chin of the fetus had to rest on one of the shoulders at all times. In his writings Smellie acknowledged the importance of Ould's observations.

After careful study Smellie described the structure and form of the female pelvis. Making a point of fundamental importance, he wrote: "From these particulars, any person will perceive the advantage of remembering that the pelvis at the brim is wider from side to side, than from the fore to the back part, whereas below it is the reverse in point of dimension; that the pelvis is much shallower at the os pubis than at the sides and the back part; and that the sacrum and coccyx form a large concave in their descent, while that of the os pubis is perpendicular." He noted that the pelvis varies from one woman to another, he described a variety of abnormal pelves, and he pointed out that the fetal head is greater from front to back than from side to side.

Smellie went on to describe the passage of the fetal head through the pelvis: "This therefore is the manner of its progression. When the head first presents itself at the brim of the pelvis, the forehead is to one side, and the hind head to the other, and sometimes it is placed diagonal in the cavity; thus the widest part of the head is turned to the widest part of the pelvis, and the narrow

part of the head, from ear to ear, applied to the narrow part of the pelvis between the pubis and the sacrum. The head, being squeezed along, the vertex descends to the lower part of the ischium where, the pelvis becoming narrower at the sides, the wide part of the head can proceed no further in the same line of direction; but the ischium being much lower than the os pubis, the hind head is forced in below this last bone, where there is least resistance. The forehead then turns into the hollow at the lower end of the sacrum, and now again the narrow part of the head is turned to the narrow part of the pelvis. The os pubis being only two inches deep, the vertex and the hind head rise upward from below it; the forehead presses back the coccyx; and the head, rising upward by degrees comes out with a half-round turn from below the share-bone; the wide part of the head being now betwixt the os pubis and the coccyx, which, being pushed backwards, opens the widest space below, and allows the forehead to rise up also with a half-round turn from the under part of the os externum."

Thus Smellie described engagement in the transverse, internal rotation, flexion, and extension. Later authors claimed that engagement was in the oblique and not in the transverse, but more recent x-ray studies have shown Smellie to be correct. He was in error in believing that the transverse diameter of the inlet is the largest, while actually it is the oblique. On the basis of his own observations and his own reasoning Smellie gave us the first accurate description of the passage of the fetal head through the pelvis. He was the second (after Ould) to question the truth of the traditional beliefs handed down from Hippocrates.

The Obstetrical Forceps.—The available instruments were mainly of destructive intent. These included the fillet or lack, a ribbonlike loop of woven material which had to be manipulated over one of the prominences of the head to provide for traction, the blunt hook, and the crochet or sharp hook which was used for both traction and dismemberment. The perforators were excessively complicated, so Smellie made a combination scissors-perforator, which because of its simplicity and effectiveness became the model for subsequent perforators. Until the advent of the forceps, any operative delivery was usually a destructive one.

The Chamberlens invented the obstetrical forceps, but Smellie taught us how to use them properly. Baudeloque had this to say: "No one had more confidence in the forceps than Smellie, no one rendered them of more general use, nor applied them more methodically or with greater success."

Smellie did not have forceps in the first 13 years of his practice, and often the child had to be destroyed before delivery could be effected. He learned of the forceps in 1735 and introduced them into his practice. The first instrument he had was the Dusé forceps, a long heavy instrument with solid blades. He was not satisfied with his early use of the forceps and set out to improve both the instrument and his technique.

Smellie invented what is known today as the English lock, but for many years it was called the Smellie lock. It is so good that it has remained unaltered to the present time. He made and used a small, light, straight forceps with a short handle. He believed that this instrument, measuring less than 12 inches, was the safest for the majority of cases. He noted that ". . . Forceps may take such firm hold, that with great force and a strong purchase the head will be delivered; but such violence is commonly fatal to the woman, by causing such an inflammation, and perhaps laceration, of the parts as is attended with mortification. In order to disable young practitioners from running such risks, and to free myself from the temptation of using too great force, I have always recommended the forceps so short in the handles, that they cannot be used with

such violence as will endanger the woman's life; though the purchase of them is sufficient to extract the head when one half or two thirds of it are equal to or past the upper or narrow part of the pelvis.''

Difficulty with the aftercoming head in breech deliveries, and with the head high in the pelvis in cephalic presentations, prompted his making a long forceps, 12½ inches longer than the short ones, and with a marked pelvic curve. He found that the curve of the forceps fitted the curve of the pelvis better than the straight ones did, and he was able to get a better grip on the head. The basic design of this instrument has not been changed to this day.

Because of the prevailing belief that the only purpose of instruments was to destroy undeliverable babies special gowns and techniques were developed so that neither the patient nor her relatives would realize that forceps were being used. To avoid the noise which metal blades made, Smellie tried wooden forceps, and then metal forceps with the blades wrapped in leather bindings. Both of these ideas proved to be impractical and unsanitary, and were given up. Smellie was accused of using forceps too often, but he maintained that he used them only when necessary, after he had given nature every opportunity to effect delivery.

Dissatisfied with current methods of using forceps, he described techniques and formulated rules for the proper use of forceps which hold good today. He remarked, ''The common way of using them formerly was by introducing each blade at random, taking hold of the head anyhow, pulling it straight along, and delivering with downright force and violence; by which means both os internum and externum were often tore, and the child's head much bruised. On account of these bad consequences they had been altogether disused by many practitioners. I began to consider the whole in a mechanical view, and reduce the extraction of the child to the rules of moving bodies in different directions. In consequence of this plan I more accurately surveyed the dimensions and form of the pelvis, together with the figure of the child's head and the manner in which it passed along in natural labours; and from the knowledge of these things, I not only delivered with greater ease and safety than before, but also had the satisfaction to find, in teaching, that I could convey a more distinct idea of the art in this mechanical light than in any other. . . .''

Some of the points which Smellie emphasized include the following: (1) every bad position of the head should be altered before the forceps are applied; (2) the blades should be applied over the ears whenever possible; (3) traction should be applied during uterine contractions, with a side-to-side movement. (4) The direction of traction must be changed as the head emerges under the symphysis. This last movement, now called extension, was first clearly demonstrated by Smellie. Thus Smellie emphasized the importance of knowing the exact fetal position, he advocated the cephalic application of the forceps, and he taught that traction must be made along the lines of direction of the pelvic canal.

Posterior Positions of the Head.—The treatment for persistent occiput posterior was podalic version. Smellie made a practice of correcting this position by hand. Later, almost by accident, he found in a case that he could not turn by hand, that he could do so with the forceps, and so became the first man to use forceps for the purpose of rotation. When he was unable to rotate the head he delivered it face to pubis.

Smellie described the delivery of posterior positions in this way: ''The blades of the forceps should be introduced along the ears, or as near them as possible, according to the foregoing directions, the head must be pushed up a little, and the forehead turned to one side of the pelvis; thus let it be brought along until the hindhead arrives at the lower part of the ischium; then the forehead must be turned backward, into the hollow of the sacrum, and even a

quarter or more to the contrary side, in order to prevent the shoulders from hitching on the upper part of the os pubis or sacrum, so that they may be still towards the sides of the pelvis; then let the quarter turn be reversed, and the forehead being replaced in the hollow of the sacrum, the head may be extracted as above."

Breech Presentation.—In his writings Smellie advised breech extraction as soon as the feet or the knees reached the cervix. He did not seem to realize that pulling on the legs too soon might cause extension of the head and the arms, and so complicate the case seriously. In his later years he recognized the wisdom of trusting to nature, and he interfered less in breech and footling presentations. On the other hand he did not, as we do today, bring down the arms before delivery of the head. He said: "Indeed, if the pelvis is not narrow, nor the head very large, and the arms lie along the sides of the head, there is seldom occasion to pull them down . . . but when . . . the head sticks in the pelvis, they ought certainly to be brought down; or even when the head comes with difficulty."

Smellie emphasized that the baby's body be turned so that the head is born with the occiput anterior, and described the manner of putting a finger in the baby's mouth to maintain flexion of the head. He gave the details of what is known today as the Mauriceau-Smellie-Veit maneuver. First the accoucheur brings down both arms. Then "If one finger of his right hand be forced in the child's mouth, let the body rest on that arm; let him place the left hand above the shoulders, and put a finger on each side of the neck; if the forehead is towards one side at the upper part of the pelvis, let him pull it lower down, and gradually turn it into the hollow of the sacrum; then stand up, and in pulling raise the body so as to bring out the head in a half-round turn." There seems to be no doubt that Mauriceau was the first to describe the Mauriceau-Smellie-Veit maneuver. We do not know if Smellie heard of Mauriceau's work, or if his was an independent finding. Certainly Smellie recommended it to England. Veit's contribution was that he made the maneuver popular in Germany. There is, however, good reason to believe that Smellie was the first to advocate forceps on the aftercoming head.

Delivery of the Placenta.—The belief at this time was that the cervix clamped down right after the birth of the baby, and that the placenta must be delivered before this happened. Some favored immediate manual removal, others preferred pulling on the cord. At first Smellie adhered to the cord-pulling school but he gradually changed his ideas, and waited to give nature a chance before interfering. He said: " . . . so, in my opinion, we ought to go the middle way, never to assist but when we find it necessary; on the one hand, not to torture nature when it is self-sufficient, nor delay it too long, because it is possible that the placenta may sometimes, though seldom, be retained several days; for if the uterus should be inflamed from any accident, and the woman be lost, the operator will be blamed for leaving the afterbirth behind."

Cesarean Section.—Smellie never did a cesarean section on a live patient. He performed three postmortem cesarean sections on women who died from placenta previa, but all the babies were born dead. He did, however, realize the possibilities of cesarean section, and said:

"When a woman cannot be delivered by any of the methods hitherto described and recommended . . . in such emergencies, if the woman is strong and of a good habit of body, the Caesarian operation is certainly advisable, and ought to be performed; because the mother and child have no other chance to be saved, and it is better to have recourse to an operation which hath sometimes succeeded, than leave them both to inevitable death. Nevertheless, if the woman is weak,

exhausted with fruitless labour, violent floodings, or any other evacuation which renders her recovery doubtful, even if she were delivered in the natural way; in these circumstances it would be rashness and presumption to attempt an operation of this kind, which ought to be delayed until the woman expires, and then immediately performed with a view to save the child."

Smellie was distressed over the number of craniotomies, and he had this to say: "Midwifery is so much improved, that the necessity of destroying the child does not occur as often as formerly. Indeed it should never be done, except when it is impossible to turn or deliver with forceps; and this is seldom the case but when the pelvis is too narrow, or the head too large to pass, and therefore rests above the brim . . . because in these two cases there is no room for hesitation; for if the woman cannot possibly be delivered in any other way, and is in imminent danger of her life, the best practice is undoubtedly to have recourse to that method which alone can be used for her preservation, namely, to diminish the bulk of the head."

False Labor.—That the problem of distinguishing false from true labor is not a new one is shown by Smellie's detailed notes on the subject. "If the os uteri remains close shut, it may be taken for granted that the woman is not yet in labor, notwithstanding the pains she may suffer. Sometimes the os internum may be a little dilated, and yet it may be difficult to judge whether or not the patient be in labour. The case, however, may be ascertained after some attendance, by these considerations. If the woman is not arrived at her full time; if no soft or glairy mucus hath been discharged from the vagina; if the pains are limited to the region of the belly without extending to the back and inside of the thighs; if they are slight, and continue without intermission or increase; nay, if they have long intervals, and recur without force sufficient to push down the waters and membranes, or the child's head, to open the os internum; if this part be felt thick and rigid, instead of being soft and thin and yielding; we may safely pronounce that labour is not yet begun."

Artificial Rupture of the Membranes.—Smellie recognized the value of artificial rupture of the membranes: "When the membranes, therefore, are strong or unadvanced, and continue so long unbroke that the delivery is retarded, provided the os internum be sufficiently dilated, they ought to be broke without further delay, especially if the woman hath been much fatigued or exhausted with labour, or is seized with a violent flooding, in which case the rupture of the membranes hastens delivery, and the haemorrhagy is diminished by the contraction of the uterus, which lessens the mouth of the vessels that are also compressed by the body of the child."

Seven- and Eight-Month Gestations.—Smellie was the first to deny that a 7 months' baby had a better chance for survival than one born after 8 months' gestation. He said: "Hippocrates alleges that a child born in the seventh month sometimes lives; whereas if it comes in the eighth month it will probably die; because all healthy children, says he, make an effort to be born in the seventh month; and if they are not then born, the nisus is repeated in the eighth, when the child must be weakened by his former unsuccessful attempt, and therefore not likely to live; whereas should the second effort be deferred till the ninth, the foetus will by that time be sufficiently recovered from the fatigue it had undergone in the seventh. Experience, however, contradicts this association; for the older the child is, we find it always the stronger, consequently the more hardy and easily nursed. Neither is there any sufficient reason for adhering to the opinion of Pythagoras on this subject, who declared that number eight is not so fortunate as seven or nine."

Other Contributions.—Included among Smellie's contributions are the following: He was the first to publish an illustration of a rachitic pelvis.

He proved the falsity of the belief that the placenta was always in the fundus of the uterus by showing that it could be anywhere.

He disproved the theory that it was harder for a woman to give birth to a dead child than a live one, by showing that the child was a passive agent, and that its being alive or dead had no effect on the labor.

He was the first to revive an asphyxiated infant by inflation of the lungs through a silver catheter.

He disproved the belief, handed down from Hippocrates, that the baby presented as a breech until the seventh month and then turned to a vertex.

Misconceptions.—There are, of course, many things which Smellie did not know or understand, and some of the things that he knew turned out to be wrong.

In company with his confreres he did not understand conception.

He did not know that the uterus is a muscular organ.

He did not divide labor into stages; this was done by Denman.

He was erroneous in advising early interference in face presentations—podalic version if high, forceps if low.

Smellie believed that menstruation was a discharge of collected blood, and that "if the flow is too seldom and in too small quantity a dangerous plenitude ensues, the plethora must be lessened by plentiful bleeding and repeated purges, and the discharge solicited by warm baths, fumigations, and exercise."

Medical Writings.—Smellie left two main works. His *Anatomical Tables* contain 39 plates. It is believed that 26 of these were drawn by Rymsdyk and 13 probably by Smellie himself. These plates show the anatomy of the pelvis and various normal and abnormal obstetrical conditions.

His *Treatise on the Theory and Practice of Midwifery*[3] consists of three volumes. The first volume is, strictly speaking, the treatise proper, and contains the substance of his lectures. In the second and third volumes are the clinical records of 531 cases, each designed to illustrate one of the subjects discussed in the first volume. The first volume was published in 1752, and the second in 1754. The third appeared in 1774, after Smellie's death, edited anonymously, as were the other volumes, by his friend Tobias Smollett. His books were most popular, and were translated into French and German during his lifetime.

Conclusion

It is difficult to describe in a few words the qualities and accomplishments which made Smellie great. He considered that industry was his chief virtue. His judgment was accurate, for he worked uncommonly hard. He had the rare power of original observation and thought, and the courage to dispute the beliefs handed down unchallenged from Hippocrates. He believed that the theory must be made to fit the facts. When the ancient theory did not agree with the facts as he saw them, he had the good sense to stick with the facts and change or discard the theory.

By this process of constant study and re-examination he arrived at his greatest and at the same time his most fundamental contribution to obstetrics—the description of the passage of the fetus through the pelvis, which forms the basis of modern obstetrics.

He taught the precise use of forceps, in accordance with the mechanism of labor and the anatomy of the pelvis.

He was the outstanding teacher of his day, and successfully combined theoretical and clinical teaching. His students came from all over the world, and the spread of his influence was immense.

Smellie was a careful student of nature's methods. He said, "I diligently attended to the course and operations of nature which occurred in my practice, regulating and improving myself by that infallible standard."

He did much to dissipate the prejudice against the man midwife, and one of the results of his efforts was the recognition of the need for efficient maternity services, and lying-in hospitals. The hospitals were built, but Smellie was never appointed to the staff of any of them.

McClintock said: "That he was a close observer and correct interpreter of nature all will admit. But more than this, he seems to have been actuated with a sincere desire for the advancement of his art, and to have been free from all narrow-minded or selfish prejudices in favour of his own improvements."

Herbert Spencer[4] wrote in 1927: "In concluding this brief account of the greatest of British obstetricians, one must make a tribute of admiration for his great achievements in circumstances which would have discouraged a less heroic man.. Without powerful friends to help him, without the advantages of a hospital clinic, but attending and teaching in the homes of the poor, by sheer devotion to his art he raised himself to the foremost position in his profession, which he enriched with many original contributions."

References

1. Glaister, J.: Doctor William Smellie and His Contemporaries: A Contribution to the History of Midwifery in the 18th Century, Glasgow, 1894, J. MacLehose.
2. Johnstone, R. W.: William Smellie, the Master of British Midwifery, Edinburgh & London, 1952, E. & S. Livingstone, Ltd.
3. Smellie, W.: Smellie's Treatise on the Theory and Practice of Midwifery, London, 1876-1878, New Sydenham Society.
4. Spencer, H. R.: The History of British Midwifery from 1650 to 1800, London, 1927, John Bale Sons & Danielsson, Ltd.

CLINICAL EXPERIENCE WITH A SYNTHETIC OXYTOCIN (SYNTOCINON*)

A Study of 50 Cases in the Third Stage of Labor

ROBERT J. LUBY, M.D., MAURICE E. GRIER, M.D.,
PIERRE W. KEITGES, M.D., AND RICHERT J. TAYLOR, M.D., OMAHA, NEB.

(From the Department of Obstetrics and Gynecology, The Creighton University School of Medicine)

THE presentation is a report of the clinical evaluation of Syntocinon (synthetic oxytocin) when used in the third stage of labor. We shall briefly discuss the history of the product, its pharmacological and toxicological properties, and present our experience with its administration to 50 consecutive obstetrical patients.

It is known that the extracts from the posterior pituitary are not pure forms: posterior pituitary injection contains about 10 units of oxytocic activity per cubic centimeter and 10 units of vasopressor activity per cubic centimeter. The two fractions, oxytocin and vasopressin, possess, respectively, oxytocic and pressor-antidiuretic activity. Nevertheless, vasopressin influences the activity of the uterus and oxytocin also influences the blood vessels.[1]

It would be ideal to obtain pure oxytocin possessing only oxytocic activity. Du Vigneaud[2] in 1953 reported the chemical structure of oxytocin, stating that it contained eight amino acids and three equivalents of ammonia, and had a molecular weight of approximately one thousand. The same year a total synthesis was achieved.[3] Recently Boissonnas and associates[4] described a new synthesis with a better yield. Further understanding of the pharmacological properties of this synthetic oxytocin meant an exhaustive study with experimentation both in vivo and in vitro.

Gyermek and Fekete,[5] in 1955, found for oxytocin which was synthesized according to du Vigneaud's method a residuum of pressor and especially antidiuretic activity. In these experiments carried out in the Sandoz Laboratories, the slight pressor and antidiuretic activity could not be attributed to a contamination with vasopressin since the characteristic amino acids of vasopressin (phenylalanine, arginine, and lysine, respectively) were not used at all in the synthesis. The important pressor and antidiuretic activities, respectively, found in therapeutic doses, are of no significance, according to these authors.

*Syntocinon for this study was furnished by Sandoz Pharmaceutical Company, Hanover, N. J.

Bosch and Käser[6] in 1956 reported the results of their experience with the synthetic oxytocin, Syntocinon, in 152 cases. They considered Syntocinon and the natural oxytocic to be fully equivalent and found the former to be free of side effects.

The pharmacological investigation of Syntocinon by bioassay was reported by Konzett and co-workers.[7] These authors compared the in vitro effects of Syntocinon with those of a stanadrd preparation of an effective pituitary powder. They found that both specific and quantitative methods for assaying oxytocin yielded consistent results and enabled exact standardization of Syntocinon. Their results were:

1. The effects of 0.05 unit each of Syntocinon and the purified natural oxytocin on tonus and amplitude of the isolated rabbit uterus were identical.

2. Syntocinon produced rhythmic contractions of the isolated strips of human uterus which lacked motility, and the effect of Syntocinon was approximately equal to that of natural oxytocin.

3. In tests on the cat uterus in situ the blood pressure remained unchanged.

4. The pressor effect of Syntocinon in dogs was about one hundred times weaker than that of posterior pituitary standard.

5. The lethal dose (LD_{50}) of Syntocinon given intravenously was more than 2,900 I.U. per kilogram as compared with 340 I.U. when preservatives were present; the lethal dose (LD_{50}) of the two commercial oxytocins was 300 and 220 I.U. per kilogram.

In 1956, a number of investigators reported the results of their experience with Syntocinon. Syntocinon was assayed against natural oxytocin: ante partum, intra partum, and post partum in approximately 300 cases.[8, 9, 10] Their conclusions were that Syntocinon was strongly oxytocic in all cases. There was no appreciable difference in the rise in blood pressure following intermittent administration of Syntocinon and the oxytocic principles of the posterior lobe of the pituitary gland. No side effects were noted. The intravenous route was most effective. Syntocinon and natural oxytocin appeared to be identical in effect on the human uterus.

Methods

The cases investigated were obtained from the clinic service at the Creighton Memorial St. Joseph's Hospital, and consisted of 50 consecutive deliveries. There was no selection, the Syntocinon was administered, 5 units intravenously and 5 units intramuscularly, with delivery of the head. This routine was used in all but 2 precipitate labors and included several cases of moderate and several of severe toxemia.

The 50 control cases were obtained from patients at Booth Memorial Hospital and from the private deliveries occurring during the time of the investigation at St. Joseph's Hospital. Oxytocics in this group included Pitocin, ergonovine maleate, and methylergonovine maleate given either in combination or alone at the time of delivery of either the head or the anterior shoulder.

All deliveries were conducted under pudendal block anesthesia with scopolamine and meperidine hydrochloride analgesia. The base line blood pressure was the average of those taken from admission to delivery. The

pressures were recorded 15, 30, and 90 minutes after the oxytocic was administered. The method of delivery of the placenta was recorded, as was the duration of the third stage. The presence or absence of Adrenalin (1:100,000) in the anesthetic solution was noted. As no attempt was made to measure the blood loss accurately no comparison is included.

In evaluating the results we have classified a 10 mm. Hg rise in systolic blood pressure as being significant; we have noted the cases in which the elevation was 20 mm. Hg or greater.

Results

Of the patients who received Syntocinon (Table I) 11, or 22 per cent, had significant elevations of blood pressure of which 3, or 6 per cent, were 20 mm. or more. Ten patients in this group had moderate or severe nonconvulsive toxemia, i.e., a blood pressure of 140/100 or more with either proteinuria or edema or both; only one had a significant elevation and that from 160/110 to 180/110. Significant blood pressure elevations were demonstrated in 21, or 42 per cent, of the control patients; of these 8, or 16 per cent, were 20 mm. or more.

TABLE I. BLOOD PRESSURE ELEVATIONS

	PATIENTS	SIGNIFICANT ELEVATIONS	ELEVATIONS OF 20 MM. HG OR MORE
Syntocinon	50	11 (22%)	3 (6%)
Controls	50	21 (42%)	8 (16%)

The average duration of the third stage of labor (Table II) was 4.7 minutes with a range of one to 37 minutes (the latter, a single case occurring in a patient with precipitate labor admitted with a retained placenta) in those receiving Syntocinon as compared to 6.0 minutes with a range of 2 to 12 minutes in the control series.

TABLE II. THIRD STAGE

	AVERAGE DURATION	RANGE
Syntocinon	4.7 minutes	1-37 minutes
Controls	6.0 minutes	2-12 minutes

The incidence of manual removal of the placenta (Table III) was 10 per cent in the study cases and 16 per cent in the control series; manual removals were performed when the placenta was not in the vaginal vault by the time the infant was cared for.

TABLE III. MANUAL REMOVAL OF PLACENTA

Syntocinon	5 (10%)
Controls	8 (16%)

In the control group, 34 patients received Adrenalin in the anesthetic solution and 18, or 53 per cent, had significant increases in blood pressure; 3, or 19 per cent, of the remaining 16 had similar changes. Forty-four patients receiving Syntocinon did not get Adrenalin and all the blood pressure elevations occurred in this group.

Of significance in considering these results is the investigation by McGinty[11] in 1956, conducted in the same institutions. He compared the vasopressor effects of various oxytocics when given intravenously in the third stage of labor. Each group of 50 patients was investigated in a manner similar to the

one described above and this included studies of Ergotrate, Methergine, Pitocin, and normal saline. In a review of this project it was felt that the blood pressure taken 15 minutes after administration would more accurately indicate the presence or absence of pressor response than the 5 minute reading reported in his survey. This further evaluation resulted in the figures noted in Table IV. In his control series receiving only saline, 6 patients had an elevation of 20 mm. Hg or more but these blood pressure readings are not available for perusal and less severe rises are therefore not known.

TABLE IV. BLOOD PRESSURE ELEVATIONS

	PATIENTS	SIGNIFICANT ELEVATIONS	ELEVATIONS OF 20 MM. HG OR MORE
Pitocin	50	16 (32%)	10 (20%)
Ergotrate	50	19 (38%)	10 (20%)
Methergine	50	21 (42%)	8 (16%)

Comment

Of particular significance is the absence of severe pressor response in the 10 toxemia patients. A review of McGinty's[11] work indicates that the average significant systolic pressure elevation 15 minutes after oxytocic administration was within the range of statistical similarity for all three groups. He emphasized, however, that there were more severe elevations in the groups given Pitocin and Ergotrate compared with none in those who received Methergine.

He mentioned that all patients were delivered with Adrenalin (1:100,000) in the anesthetic solution; and suggested that this might have some relation to the blood pressure changes observed.

Also suggestive is the fact that 53 per cent of the control patients in this study receiving Adrenalin demonstrated a significant blood pressure elevation compared to 19 per cent of those who did not receive it. The number in this group is not significant for statistical analysis but if all the cases, both McGinty's and those reported above are combined, some interesting facts appear: in 184 patients who received Adrenalin (Table V), the number of significant blood pressure elevations was 74, or 40 per cent; in 60 patients who did not receive Adrenalin the number of significant blood pressure elevations was 13, or 22 per cent.

TABLE V. BLOOD PRESSURE ELEVATIONS

	PATIENTS	SIGNIFICANT ELEVATIONS
Adrenalin	184	74 (40%)
No Adrenalin	60	13 (22%)

The results of the two group comparisons, first, Syntocinon and the controls, and, second, the patients with and without Adrenalin, were subjected to analysis by means of the null hypothesis. It may be said that if these experiments were repeated indefinitely under the same conditions a smaller difference between the groups compared would occur but one time out of a hundred.*

*It was hypothesized that there was no significant difference in the blood pressure elevation between the experimental and control groups and likewise between the group receiving Adrenalin and those who did not receive it. This null hypothesis was tested by the use of the chi-square technique. In the first group a chi square of 9.345 was obtained, which is greater than the chi square of 9.210 needed at the 1 per cent level of confidence. Similarly, in the Adrenalin comparison a chi square of 6.797 was obtained which is greater than the chi square of 6.635 needed at the 1 per cent level of confidence.

Thus, the null hypothesis can be rejected and it may be said that if these experiments were to be repeated under the same conditions the possibility of a smaller difference between the groups would be one time out of a hundred.

Summary and Conclusions

1. A study of the action of Syntocinon was performed on 50 consecutive clinic patients from Creighton Memorial St. Joseph's Hospital, with reference to the presence or absence of pressor responese, duration of the third stage, and incidence of manual removal of the placenta.

2. Fifty cases from Booth Memorial and Creighton Memorial St. Joseph's Hospitals served as controls.

3. There was a significant difference in the incidence of blood pressure elevation 15 minutes after administration of the various oxytocics. Elevation occurred in 22 per cent of the patients who received Syntocinon as compared to 42 per cent of the controls who received other oxytocics.

4. In our experience Syntocinon is safe to administer intravenously in 5 unit doses to pre-eclamptic patients at the time of delivery of the head.

5. Its use with delivery of the head effectively shortens the duration of the third stage of labor.

6. There was no significant difference in the incidence of manual removal of the placenta.

7. Patients who received Adrenalin (1:100,000) in local anesthetic solution have a significantly higher incidence of blood pressure elevation.

References

1. Drill, V. A.: Pharmacology in Medicine, New York, 1954, McGraw-Hill Book Company, Inc.
2. du Vigneaud, V., Lawler, H. C., and Popenoe, E. A.: J. Am. Chem. Soc. **75**: 4880, 1953.
3. du Vigneaud, V., Ressler, C., Swan, J. M., Roberts, C. W., Katsoyamis, P. G., and Gordon, S.: J. Am. Chem. Soc. **75**: 4879, 1953.
4. Boissonnas, R. A., Guttmann, S., Jaquenoud, P. A., and Waller, J. P.: Helvet. chim. acta **38**: 1491, 1955.
5. Gyermek, L., and Fekete, G.: Experientia **11**: 238, 1955.
6. Bosch, K., and Käser, O.: Gynaecologia **141**: 228, 1956.
7. Konzett, H., Berde, B., and Cerletti, A.: Schweiz. med. Wchnschr. **86**: 226, 1956.
8. Bainbridge, M. N., Nixon, W. C., Schild, H. O., and Smyth, C. N.: Brit. M. J. **1**: 1133, 1956.
9. Bosch, K., and Käser, O.: Schweiz. med. Wchnschr. **86**: 229, 1956.
10. Francis, H. H., and Francis, W. J. A.: Brit. M. J. **1**: 1136, 1956.
11. McGinty, L. B.: West. J. Surg. **64**: 22, 1956.

CESAREAN SECTION IN THE TREATMENT OF PLACENTA PREVIA

A Review of 99 Cases

KAIGHN SMITH, M.D., PHILADELPHIA, PA.

(From the Department of Obstetrics and Gynecology, Hospital of the University of Pennsylvania)

THE modern active treatment of placenta previa began in the first quarter of this century. In his *Textbook of Obstetrics* published in 1923, Williams[1] advised the use of the intraovular balloon or Braxton Hicks version. He stated, "Thus far, only two cesarean sections have been done on our service for placenta previa." During this era statistics showed a 10 per cent maternal mortality with a fetal mortality varying from 40 to 70 per cent. The maternal death rate from central placenta previa was 25 per cent. Quite naturally, therefore, attention was first directed toward preservation of the mother's life.

In 1927 Bill[2] advocated the use of prophylactic blood transfusion and cesarean section. He presented 101 cases divided into two groups. The first 45 cases were treated prior to 1921. Blood transfusion was used only as a last resort, and 27 (60 per cent) had cesarean section. There was a maternal mortality of 11 per cent and a fetal loss of 37 per cent. The second group consisted of 56 patients treated after 1921 up to 1926. Transfusion was used liberally as a precaution, and 40 (70 per cent) had cesarean section. Fetal mortality declined only to 32 per cent on this management but there was only one maternal death.

With the advent of more frequent blood transfusion, adequate anesthesia, and the increasing use of cesarean section, the maternal mortality began to fall. But during these years, the dictum had arisen that once placenta previa was diagnosed, the pregnancy must be interrupted immediately. As late as 1945, Stander's[3] *Textbook of Obstetrics* stated, "On account of the danger of profuse and unexpected hemorrhage, pregnancy or labor, as the case may be, should be terminated in the most conservative manner as soon as possible." By then, however, the maternal danger had fallen so low that attention could be turned toward the fetus. This attention, evidenced in 1945 by two important contributions toward fetal salvage, was manifested simultaneously in Scotland by C. H. G. MacAfee,[4] and in this country by Herman W. Johnson.[5] Both minimized the dangers of bleeding in placenta previa provided that no vaginal manipulation was carried out, and refuted the dictum that there is

no expectant plan of treatment for placenta previa. In 1948, Williams[6] emphasized the importance to fetal survival of delay in delivery until maturity is attained.

Since that time, the principles of expectant management have been generally accepted and have been combined with a rising incidence of cesarean section. The advent of chemotherapy has lowered the dangers of abdominal delivery still further, and has spurred its increased use. With the rise in cesarean section has come a decline in fetal mortality. Hu[7] reported a fetal mortality of 13.5 per cent in 51 cases with 60 per cent cesarean sections. Beilly[8] had 90 per cent cesarean sections in 91 cases, with a fetal mortality of 9.8 per cent, and Kern[9] in 129 cases, doing 70 per cent cesarean sections, had a fetal mortality of 12.9 per cent.

On the other hand, there are still advocates of "conservative" management of placenta previa. For instance, Fitzgerald and associates,[13] in 1954, reported 283 cases, with 80.6 per cent vaginal deliveries. The conclusion of the paper was that 93 per cent of the infants over 32 weeks' gestation were born alive. A look at the statistics, however, shows that there were 2 maternal deaths and a gross fetal mortality of 41 per cent. Furthermore, 12 per cent of the infants alive on admission and over 28 weeks' gestation died during labor. Another 13 per cent died during the neonatal period. This is twice the death rate reported by the advocates of cesarean section as the treatment of choice.

The most recent report of a large series concerns a 35 year study by Reich[10] in which the material is divided into two groups, those treated from 1919 to 1941, and those from 1941 to 1954. In the latter years, modern principles of management, including expectant treatment and adequate blood replacement, were in force. There were 117 patients in this latter group; 85 per cent had cesarean section, with a gross fetal mortality of 26.5 per cent. Correcting the figures for infants with no fetal heart tones on admission, and those that weighed less than 1,000 grams at birth, the figure for mortality in the infants delivered vaginally was 17.6 per cent, while in cesarean section it was 10.1 per cent.

No review is complete without mention of another important advance in the study of placenta previa—Stallworthy's[11] concept of the "dangerous placenta," published in 1951. In 170 cases of placenta previa, he found 50 per cent lying on the posterior surface of the lower uterine cavity. His concept that this type of placenta particularly creates a relative cephalopelvic disproportion, and is more likely to lead to cord compression has been accepted. Because of this, he states, "It can be diagnosed in time to save the fetus, and is an indication for cesarean section."

In summary, a brief review of the literature indicates that the management of placenta previa has progressed through two phases. First, emphasis was placed through necessity on the maternal safety, with efforts to tamponade the bleeding area by balloon or Braxton Hicks version. When blood transfusion was introduced, it was used in conjunction with early delivery by

whatever method indicated, and was successful in driving maternal mortality down. The second phase began in 1945 when concern over jeopardy of the fetus became allied to that of the mother, and expectant treatment came to be utilized if it was warranted by the mother's condition. The argument over the method of delivery has persisted throughout these phases and deserves further consideration.

Material

In the present study, deliveries of the 5 year period between Sept. 1, 1951, and Aug. 31, 1956, at the Hospital of the University of Pennsylvania are covered. During this time, in 13,042 deliveries, 99 cases of placenta previa occurred, an incidence of 1:132. The rather high rate reflects not only an awareness in diagnosis, but also the inclusion of 56 cases diagnosed as low-lying placenta. Without these, the occurrence becomes 1:303, a figure very close to that of Reich, who had an incidence of 1:310 over a 35 year period, using the same criteria.

Since a marginal placenta with the cervix closed becomes partial with dilatation, both types are called partial. Had labor and dilatation been allowed in all the 56 cases of low-lying placenta, it is likely that many of these would also have become partial in position.

Results

Table I shows the method used in the diagnosis of placenta previa in this series. Of the 99 cases, 32 were diagnosed because of bleeding alone. Of these, 21 were subsequently proved at cesarean section. The remaining 11 are accepted in the series because of painless vaginal bleeding and definite evidence from examination of the membranes after vaginal delivery that the placenta was low lying. The shortest width of membranes from the point of rupture to the edge of the placenta was in no instance greater than 2 cm. Twenty-six cases were diagnosed with the aid of x-ray examination. Of the 37 x-rays of the placental site taken in cases of proved placenta previa 31 were correctly interpreted, an accuracy of 83 per cent. In 6 instances, the placenta was reported to be in the fundus and later proved to be placenta previa. The diagnosis was made by vaginal palpation in 33 cases but not without danger. As indicated in Table II, twelve patients lost significant amounts of blood from the examination alone, and 6 lost enough that, if adequate facilities had not been available, shock levels of blood pressure most likely would have been reached. The lack of vaginal examination does not insure against hemorrhage. Sixty-one patients lost up to 500 c.c. of blood not in any way connected with examination; 12 lost between 500 and 1,000 c.c., and 7 lost over 1,000 c.c., 3 of whom were admitted in shock. Otherwise, blood pressure levels were well maintained.

TABLE I. METHOD OF DIAGNOSIS OF PLACENTA PREVIA

METHOD	TYPE OF PLACENTA PREVIA		
	LOW LYING	CENTRAL OR PARTIAL	TOTAL
Bleeding alone	25	7	32
Vaginal examination	7	26	33
X-ray examination	16	10	26
At cesarean section	5	—	5
Palpation at third stage	3	—	3
Total	56	43	99

TABLE II. BLEEDING PRODUCED BY EXAMINATION IN PLACENTA PREVIA

EXAMINATION	TYPE OF PLACENTA PREVIA		
	LOW LYING	CENTRAL OR PARTIAL	TOTAL
No. of patients examined	48	38	86
No. of patients with bleeding resulting from examination	4	8	12
Blood loss of 500 c.c or more	1	5	6

Table III shows the location of the placenta on the uterine wall. It is interesting that 42 per cent of the partial and low-lying placentas were implanted on the posterior wall. Of these 33 patients with so-called Stallworthy placentas, 5 were delivered vaginally with one neonatal death, that of a previable infant of 600 grams. Twenty-eight, or approximately 85 per cent, had cesarean sections with the loss of 2 fetuses one of whom was previable, section being carried out in the interest of the mother because of constant bleeding. Five infants developed distress without ruptured membranes and cesarean section was done in all of these cases for this reason. Two patients had no bleeding during the antenatal course, but fetal distress with fundal pressure was discovered before admission. In contrast to this, with anterior placenta previa, fetal distress did not occur except in association with ruptured membranes and prolapsed cord. These figures indicate that, as Stallworthy stated, posterior low-lying placenta previa predisposes to fetal distress.

TABLE III. LOCATION OF PLACENTA

LOCATION	TYPE OF PLACENTA PREVIA		
	LOW LYING	PARTIAL	TOTAL
Posterior wall	20	13	33
Anterior wall	15	5	20
Lateral wall	5	2	7
Over the os (central)	—	—	23
Not stated	16	—	16
Total	56	20	99

The principles of expectant management were adopted by the University Hospital in the years preceding the present study. Of the 99 patients studied, 40 spent more than 2 days in the hospital, and 12 were not delivered for over 2 weeks following diagnosis. An attempt was made to delay delivery until at least the thirty-sixth week of gestation unless the maternal hazard from excess bleeding forced interruption.

The method of delivery of these patients is indicated in Table IV. The cesarean section rate of 61 per cent in cases of low-lying placenta and 91 per cent in central and partial placenta previa is one of the highest recorded. Vaginal delivery was reserved for minor degrees of placenta previa, or cases in which hope for survival of the infant was minimal. Only one potentially viable infant in the central and partial group was delivered vaginally. This patient had developed vaginal spotting as her only symptom. Twelve hours later spontaneous labor and delivery of a living 3,400 gram infant ensued. The total amount of blood lost including ante partum was estimated to be 200 c.c. Of the 3 other infants in this group delivered vaginally 2 were previable infants at 20 and 22 weeks' gestation, and one a macerated stillborn infant with no fetal heart tones on admission. Eliminating these 3 from the statistics, the cesarean section rate in central and partial placenta previa becomes 97 per cent.

TABLE IV. METHOD OF DELIVERY

DELIVERY	TYPE OF PLACENTA PREVIA					
	LOW LYING		CENTRAL OR PARTIAL		TOTAL	
	NO.	%	NO.	%	NO.	%
Vaginal	22	39	4	9	26	26
Cesarean section	34	61	39	91	73	74
Total	56		43		99	

Even in patients with low-lying placentas, vaginal delivery occurred only when surgery was contraindicated, the outcome for the fetus was hopeless, or the patients had mild symptoms. Seventeen of the 22 patients with low-lying placentas who were delivered vaginally had nothing more than either vaginal spotting prior to labor or excess bloody show in labor. Of the remaining 5, one had a previable infant, one had no fetal heart tones on admission, one was admitted in shock, operation being therefore contraindicated, and 2, after an initial hemorrhage, had complete subsidence of bleeding in the hospital, followed by spontaneous labor with no further hemorrhage at 36 and 37 weeks' gestation. That the high rate of cesarean section in both these groups has a rational basis is shown by equally good fetal salvage both in the minor cases with vaginal delivery and in the cesarean section group, with more severe forms of placenta previa.

Transverse lower uterine segment cesarean section was favored, as indicated by the fact that 54 of the 73 operations were of this type. In 10 instances, the incision was made over the placenta. In an attempt to avoid this complication, 19 operations were of the low corporeal, or classical type. Five of these, however, involved incision of the placental site, and were therefore not successful in their purpose. Of the 15 operations done through the placental site, 3 were accompanied by a blood loss of 1,000 c.c. or more at operation and in one of these the blood loss was 2,000 c.c. In this one, the operative note contains the statement that cutting through the placenta resulted in severe hemorrhage. There were 4 fetal deaths in this group. One fetus was previable, one was the second of premature twins, and of the other 2, one died of hyaline membrane disease and the other of prematurity atelectasis after 2 days. The series is too small to be significant, but it is a high death rate compared with that of the over-all series. The placenta should be avoided if possible. If encountered the operator must go around and not through it.

TABLE V. INDICATIONS FOR CESAREAN SECTION

INDICATIONS	TYPE OF PLACENTA PREVIA		
	LOW LYING	CENTRAL OR PARTIAL	TOTAL
Maternal.—			
Continued or profuse bleeding	18	15	33
Previous bleeding, quiescent	3	23	26
Previous cesarean section	4	—	4
Fetal.—			
Fetal distress	7	1	8
Malpresentation	2	—	2
Total	34	39	73

The primary indication for cesarean section is shown in Table V. The sections for bleeding were emergency operations. The patients who had no bleeding at operation were those scheduled for cesarean section who had been

in the hospital with subsidence of the bleeding. They were operated upon near term in the interest of the mother and for the survival of the fetus. No patient with central or partial placenta previa whose bleeding had subsided was allowed to labor, and vaginal delivery was permitted in only 4 of 18 patients with low-lying placentas and viable infants diagnosed before labor started. The others had cesarean section; 2 were allowed a trial of labor, before excess bleeding created the necessity for abdominal delivery.

The morbidity in the entire group was 20 per cent; 13 per cent of this was febrile morbidity. Ten instances of postpartum deciduitis, 5 of urinary tract infection, 2 of postoperative ileus, and one wound dehiscence followed these deliveries. There was no maternal death.

Fetal Results

Since maternal death is now rarely a problem, fetal salvage has become a major consideration in placenta previa. In this series there were 2 sets of twins, so there were 101 infants, 26 delivered vaginally and 75 by cesarean section. By either route, much of the infant's chance of survival depends to a large extent upon his weight and the duration of pregnancy. These figures were indicated by Tables VI and VII. To justify cesarean section in all but the most minor forms of placenta previa, there must be an indication that infant lives are saved out of proportion to the increased risk to the mothers. In this series, over one half of the patients were delivered in the last month of pregnancy. All of the infants alive on admission over 35 weeks' gestation survived except one. This was the second of twins, and weighed 1,400 grams, while the surviving twin weighed 1,430 grams. *All of the infants over 2,500 grams survived.* These figures show the rationale of cesarean section in placenta previa.

TABLE VI. FETAL MORTALITY IN RELATION TO DURATION OF GESTATION

WEEKS OF GESTATION	TOTAL INFANTS	NO FETAL HEART SOUNDS ON ADMISSION	DIED AFTER ADMISSION	% MORTALITY
Before 28	10	2	8	100
28-32	9	0	8	89
33-34	16	0	3	19
35-36	14	0	1	7
37-38	24	2	0	8
39-term	28	0	0	0
Total	101	4	20	23.8

TABLE VII. FETAL MORTALITY IN RELATION TO INFANT WEIGHT

INFANT WEIGHT IN GRAMS	TOTAL INFANTS	NO FETAL HEART SOUNDS ON ADMISSION	DIED AFTER ADMISSION	% MORTALITY
Up to 1,000	12	2	10	100
1,000-1,500	3	0	2	67
1,500-2,000	16	1	6	44
2,001-2,500	14	1	2	21
Over 2,500	56	0	0	0
Total	101	4	20	23.8

Infants that weigh less than 1,000 grams continue to be an enigma to obstetricians and pediatricians alike. A mortality rate of 100 per cent is not unusual. Infants larger than this have a significantly higher chance for survival in normal pregnancies and delivery than the figures shown in this series.

According to Holt's *Pediatrics*[12] infants between 1,000 and 1,500 grams should have a 50 per cent chance of survival, those between 1,500 and 2,000 grams 80 per cent, and between 2,000 and 2,500 grams 90 per cent.

Of the 20 infants who died after admission, 2 died during labor and 18 in the neonatal period. One of the 2 that died during labor was a previable baby of 700 grams. The other weighed 1,540 grams, was in a compound presentation, and was delivered by internal podalic version and Dührssen's incisions because of fetal distress. It took 8 minutes to deliver the head. How much better if this baby had been born by cesarean section?

Even though the mortality figures are good, there is room for more improvement. Perhaps the intrapartum death described is a case in point. The other and more important consideration, however, is that the principles of expectant management were not maintained in every instance. Five cesarean sections were done for placenta previa at less than 34 weeks, with intact membranes, no labor, and an estimated preoperative blood loss of less than 250 c.c. In this group there was one set of twins, both of whom lived. Three of the other 4 babies died, one of hyaline membrane disease, and 2 of prematurity. It is easy to conjecture that, had these sections been delayed until the thirty-fifth week or later, our fetal mortality rate would be even lower.

Table VIII shows the corrected fetal mortality rate after deletion from the gross statistics of the infants with no fetal heart tones on admission and those under 1,000 grams. The total corrected mortality of 11.5 per cent compares favorably with that of any series yet published. That the mortality rate is as low in the cesarean section group which had the major types of placenta previa as it is in the minor grades of low-lying placenta treated by vaginal delivery is an indication that fetal mortality rates even in severe placenta previa can be brought to a minimum by the frequent use of cesarean section in all but the mildest types.

TABLE VIII. CORRECTED FETAL MORTALITY

	METHOD OF DELIVERY		TOTAL
	VAGINAL*	CESAREAN SECTION	
Infants delivered	26	75	101
Died	10	14	24
Previable	4	6	10
No fetal heart sounds on admission	4	0	4
Gross mortality (%)	39	19	24
Corrected mortality (%)	11.1	11.6	11.5

*Vaginal delivery reserved for minor forms of low-lying placenta.

The causes of fetal death were not significant. Of the 10 infants viable on admission who died, 6 died of prematurity, 3 of hyaline membrane disease, and the intrapartum death of the other has been described.

Summary and Conclusions

1. A brief review of the literature on placenta previa has been presented, with emphasis on the increasing use of cesarean section and its rationale.

2. The figures from the Hospital of the University of Pennsylvania show as high a cesarean section rate as any in the literature and a corrected mortality rate (11.5 per cent) which supports this method of management.

3. Vaginal delivery was reserved for cases of low-lying placenta of the most minor degrees, those in which the chance for survival of the infant was hopeless, or in which surgery was contraindicated.

4. With improved facilities for anesthesia, blood transfusion, and pre- and postoperative care available, a high cesarean section incidence in this complication of pregnancy is to be accepted as rational therapy.

5. An important pitfall in such therapy is the tendency to operate too soon. The 3 infant deaths in the cases with little blood loss, no labor, and intact membranes, in which operation was performed before the thirty-fourth week of pregnancy show this clearly.

6. Operation in the fetal interest must be delayed until term approaches, except when the mother is put in jeopardy by continued bleeding.

7. If this is accomplished and the baby reaches 2,500 grams, fetal survival should be 100 per cent as it was in this experience.

References

1. Williams, J. W.: Williams Obstetrics, ed. 5, New York, 1923, D. Appleton & Co.
2. Bill, A. H.: Am. J. Obst. & Gynec. **14**: 523, 1927.
3. Stander, H. J.: Textbook of Obstetrics, New York, 1945, Appleton-Century-Crofts, Inc.
4. MacAfee, C. H. G.: J. Obst. & Gynaec. Brit. Emp. **52**: 313, 1945.
5. Johnson, H. W.: Am. J. Obst. & Gynec. **50**: 248, 1945.
6. Williams, T. J.: Am. J. Obst. & Gynec. **55**: 169, 1948.
7. Hu, H.: J. Am. M. Women's A. **9**: 143, 1954.
8. Beilly, J. S., Greenberg, M. W., Aaron, J. B., and Peck, S. J.: Am. J. Obst. & Gynec. **63**: 414, 1952.
9. Kern, F. M.: S. Clin. North America **34**: 1523, 1954.
10. Reich, A. M.: Am. J. Obst. & Gynec. **72**: 277, 1956.
11. Stallworthy, J.: Am. J. Obst. & Gynec. **61**: 720, 1951.
12. Holt, L. E., Jr., and McIntosh, R.: Holt Pediatrics, ed. 12, New York, 1953, Appleton-Century-Crofts, Inc.
13. Fitzgerald, J. E., Webster, A., Geittmann, W. F., and Zummo, B.: Am. J. Obst. & Gynec. **68**: 659, 1954.

PLACENTA PREVIA: THE ROLE OF CONSERVATIVE MANAGEMENT IN A CONTROLLED STUDY*

JAMES P. SEMMENS, COMMANDER (MC) USN**

(From the Department of Obstetrics, U. S. Naval Hospital, Portsmouth, Virginia)

FROM Jan. 1, 1954, to June 1, 1957, 166 cases of placenta previa which occurred in 18,408 deliveries were studied as part of an over-all fetal mortality evaluation at the U. S. Naval Hospital, Portsmouth, Virginia. This significant number of cases in a relatively short time permitted an evaluation of strict conservative management with (1) adequate amounts of readily available blood, (2) newer broad-spectrum antibiotics, and (3) recently improved radiological diagnostic techniques. Certain acceptable methods of diagnosis and treatment were found to have margins of error and dangers limiting their usefulness. To some physicians, conservative management means only a period of observation with specific plans to effect delivery by cesarean section at the onset of the next bleeding episode, when blood and operating facilities are more readily available; whereas it should mean the prolongation of intrauterine gestation for the infant, support of the maternal circulation, and delivery at the time and by the method that best serve the interests of the mother and infant. Time permits a more accurate diagnosis and allows for selection of the optimum method of delivery, protecting the mother and the fetus in the current pregnancy and offering a better maternal prognosis for future pregnancies. These inherent benefits of conservative management have prompted this report.

Material and Sources

During the 41 months' study, there were 18,408 deliveries on our Obstetrical Service. All cases of bleeding after the twentieth week of gestation were considered. The diagnosis of placenta previa in all cases was made by one or more of the following methods: (1) x-ray, either by soft-tissue technique or air cystograms; (2) sterile vaginal examination, usually with double setup; (3) visualization of the placental site at the time of cesarean section; and (4) visualization or palpation of the placenta through the dilated cervix at delivery.

Classification

The classification[5, 20] of placenta previa employed is that recommended by Greenhill, Titus, McCormick, and Eastman in 1949, namely, total, partial, and low lying or marginal.

*The opinions or assertions contained herein are the private ones of the author and are not to be construed as official or reflecting the view of the Naval Service at large.

**Present address Department of Obstetrics and Gynecology, U. S. Naval Hospital, U. S. Naval Base, Charleston, S. C.

Incidence

Our over-all incidence of placenta previa was found to be 0.92 per cent or 1:109 deliveries. As shown in Table I, Schmitz[20] is the only author with more than 1:200 in a single series. Eastman's text points out that Berkeley, collecting 5,000 cases in 17 different British hospitals, reported an incidence of 1:98.

The types of placenta previa occurring in this study were: 43 cases of total (25.9 per cent); 56 cases of partial (34.9 per cent); and 65 cases of low lying (39.2 per cent), of which 13 were low lying posterior (so-called "dangerous placentas"). The special significance of this type will be discussed later under treatment and methods of delivery. Reviewing Table II, the four authors[4, 5, 13 and 14, 20] reporting the bulk of cases in the literature (5,175 cases) report total placenta previa in 23 to 31 per cent of cases or an average of 26 per cent. Another group of authors[3, 10, 11] (409 cases) report total placenta previa in 37 to 41 per cent of cases. The variables are in the number of partial and low lying placenta previas reported. Labor is a factor, as a laterally implanted placenta in the lower uterine segment may be diagnosed as partial without labor or low lying with labor, and a total without labor may prove to be a partial with labor and retraction of the lower uterine segment.

Table I. Incidence of Placenta Previa

AUTHOR	PERIOD UNDER STUDY	NO. OF DELIVERIES	NO. OF CASES	RATIO	%
Beilly[2]	1940-1950	34,548	162	1:212	0.47
Berkeley (Eastman)[5]			5,000	1:98	0.98
Davidson	1950-1955	32,505	137	1:235	0.42
Eadie and Randall[4]	1954	26,136	131	1:200	0.50
Johnson[14]	1939-1950	50,000	201	1:250	0.32
Hibbard[11]	1947-1954	48,143	213	1:226	0.42
Schmitz[20]	1941-1951	17,745	112	1:158	0.60
Hatten, Kirkpatrick and Thornton[10]	1947-1954	13,236	59	1:224	0.44
Semmens (this study)	1954-1957	18,408	166	1:109	0.92

Table II. Incidence of Placenta Previa by Type

AUTHOR	NO. OF CASES	TYPE OF PLACENTA PREVIA		
		TOTAL %	PARTIAL %	LOW LYING %
Beilly[2]	162	51.8	42.0	6.0
Berkeley (Eastman)[5]	4,508	23.6	20.7	55.7
Davidson[3]	137	39.0	14.0	51.0
Eadie and Randall[4]	131	24.5	20.6	54.9
Eastman[5]	304	23.0	29.0	48.0
Hatten, Kirkpatrick and Thornton[10]	59	37.0	17.0	46.0
Hibbard[11]	213	40.8	21.8	37.5
Johnson[13, 14]	120	28.0	18.0	42.0
Schmitz[20]	112	31.3	26.7	42.0
Semmens (this study)	166	25.9	34.9	39.2
			Low lying posterior	8.0

Placenta previa is a complication that favors the multipara 4:1 or more. This is borne out in all studies, as reported in Table III; Johnson[14] reports 76 per cent, Schmitz[20] 80 per cent, and Hibbard[11] more than 90 per cent. Our incidence of multiparity was 78.3 per cent, with one in 10 a grand multipara. Primigravidas (normally 40 per cent of the obstetrical population on our service) accounted for only 21.7 per cent of the placenta previas. The average age of our patients was 24.5 years, while Eastman[5] states that Strassmann found the average age of his patients to be 32.9 years, with an average of 6.38 labors.

TABLE III. PARITY OF PATIENTS WITH PLACENTA PREVIA

AUTHOR	TOTAL NO. CASES	PRIMIGRAVIDAS %	MULTIPARAS %	GRAND-MULTIPARAS %
Hibbard[11]	213	10.0	90.0	—
Johnson[14]	120	24.0	76.0	—
Schmitz[20]	112	20.0	80.0	—
Semmens (this study)	166	21.7	78.3	7.2

Onset of First Significant Bleeding

The early onset of significant bleeding is the basis of the rationale for conservative management. Twenty-five patients were admitted to the service bleeding before the thirtieth week of gestation and another 25 were admitted before the thirty-third week. Thus *one-third* of all our patients depended upon continued intrauterine gestation for increased fetal salvage. Twenty-one of these patients could have been delivered of previable fetuses, yet there were only 13 infants delivered weighing less than 1,000 grams, and 2 of these survived. The 10 infants who lived must be considered salvaged primarily because their delivery occurred at a more advanced period of gestation.

The intermediate group (34 to 37 weeks) also has a better prognosis if delivery can be delayed at least until the maternal circulation has been stabilized; however, many of these patients are delivered shortly after admission because labor is well established and continuing blood loss threatens the fetus with anoxia.

The time of onset of bleeding in other studies of placenta previa is compared in Table IV. It is significant that Eadie and Randall[4] reported a 77.1 per cent incidence of bleeding before the thirty-seventh week, attended by a 43.2 per cent uncorrected fetal mortality. Our series showed 53 per cent before the thirty-seventh week and a 15.9 per cent uncorrected fetal mortality.

TABLE IV. ONSET OF BLEEDING ASSOCIATED WITH PLACENTA PREVIA

TIME OF ONSET	EADIE AND RANDALL[4] %	SEMMENS (THIS STUDY) %	SCHMITZ[20] %
Prior to Third Trimester.—			
22-28 weeks	17-12.9	15- 9.0	
22-31 weeks			8- 7.0
Third Trimester.—			
28-30 weeks	19-14.5	6- 3.6	
31-33 weeks	21-16.0	25-15.1	
31-38 weeks			38-33.0
34-37 weeks	39-29.7	42-25.3	
38-40 weeks	25-19.1	32-19.3	66-60.0
Term—Active Labor.—			
40 weeks plus	5- 3.8	46-27.7	

Presentations

There were 21 transverse lies (12.6 per cent) which is *35 times* the incidence (0.34 per cent) expected with a normally implanted placenta. There were 21 breech presentations (12.6 per cent) which is *3 times* the normal expected rate. Only 2 of the transverse lies occurred in a second twin. Of 124 vertex presentations (74.8 per cent), there were 3 brows and 3 occiput posteriors.

Management

The management of third-trimester bleeding consists of four distinct phases. The first is that rendered in the home: no rectal examinations, no vaginal examinations, *no packing,* immediate hospitalization, preferably by ambulance.

The second phase is undertaken at the time of admission to the hospital and includes: (1) abdominal examination noting rigidity, or localized tenderness, station, and presentation; (2) bed rest and observation unless the bleeding is brisk and fails to abate and shock threatens; (3) typing and crossmatching for anticipated blood loss; (4) base line hemoglobin, hematocrit, and red blood count; (5) No. 18 needle in a vein with fluids running; (6) nothing by mouth (liquids and soft diet are not offered until bleeding has ceased for 24 hours); (7) fibrinogen levels (Schneider method) when abruptio placentae is suspected, and smears for nucleated red cells if vasa previa is a possibility.

In the third phase of treatment the patients may be divided into two groups: (1) Those who continue to bleed and threaten to go into shock are examined under sterile double setup and delivered by the safest and most expedient method. (2) Those who stop bleeding under the regime outlined in phase two are evaluated by x-ray placentography after a short time interval (preferably after the thirty-second week). Vaginal examinations are deferred when the x-ray is positive for, or highly suggestive of, placenta previa and unless the pregnancy is beyond 37 weeks. Patients are examined vaginally only when the period of gestation favors delivery in preference to observation (38 weeks) or when bleeding recurs, necessitating the selection of a method of delivery. All patients with negative placentograms are examined vaginally, by speculum and digitally, treated, and discharged.

The election of the method of delivery might be considered as the fourth phase of management. It is based on the condition of the cervix and the degree of placenta previa present. In the long, closed cervix (characteristic of the nullipara), patients with total and partial placenta previa are usually delivered by cesarean section if near term. Low lying placenta previa is treated by artificial rupture of the membranes, allowing the presenting part to tamponade the placenta in the lower uterine segment. Failure of the presenting part to engage, as is common in low lying posterior placenta previa, is usually attended by excessive bleeding and cesarean section is essential. The short soft cervix (characteristic of the multipara) lends itself to vaginal delivery in partial placenta previa and low lying placenta previa once the membranes have been ruptured. All patients with total placenta previa and occasional patients with partial placenta previa who continue to bleed are delivered by cesarean section.

Ideally, (1) the maternal systolic blood pressure should be 90 mm. Hg or higher at the time of operation, (2) the placenta should be separated rather than perforated, (3) the cord should be clamped immediately following delivery, (4) blood counts should be taken on all babies and anemia treated early by transfusion, (5) all unnecessary intrauterine manipulation should be avoided, including manual removal of the placenta, (6) there should be prompt delivery once dilatation is complete, occiput posteriors rotated, and low forceps employed when spontaneous delivery is not imminent.

Diagnostic Aids

X-ray.—Good x-ray technique is imperative in conservative management. A poor technique or false negative film may cause the patient to be subjected to

vaginal examination at a time when incited bleeding could force delivery of an immature or premature infant. A total of 200 placentograms were taken during the interval of the study, 63 of these on patients with placenta previa proved clinically during labor or at delivery. The placenta was identified in the lower uterine segment in 59 of these cases (93.7 per cent). The exact type of placenta previa was diagnosed by x-ray in 52 cases (82.5 per cent). In 7 cases localization of the placenta was inconclusive as to type (6 were total and 1 was a partial). Of 141 cases reported as negative, only 4 reports were proved to be in error (2 were partial and 2 were low lying placenta previa). This is an over-all accuracy of 98 per cent (Table V). Hibbard[11] reported 90 per cent positive placental identification by x-ray in his series. Seventeen air cystograms were taken when soft-tissue technique failed to give definite placental localization and placenta previa was strongly suspected. All were positive and the localization was 100 per cent accurate, as confirmed at delivery.

TABLE V. EMPLOYMENT OF PLACENTOGRAPHY AS A DIAGNOSTIC AID IN THE CONSERVATIVE MANAGEMENT OF PLACENTA PREVIA AT THE U. S. NAVAL HOSPITAL, PORTSMOUTH, VIRGINIA

				NO.	%
Total placentograms taken during study				200	
Total placentograms reported as negative for placenta previa				141	
Total number of patients with clinically proved placenta previa who had placentograms				63	
Erroneous diagnosis				4	2.0
Positive clinically, negative x-ray			4		
Partial placenta previa		2			
Low lying placenta previa		2			
Negative clinically, positive x-ray			0		100.0
Placenta identified in lower uterine segment				59	93.7
Actual type of placenta previa by x-ray				52	82.5
Inconclusive as to type of placenta previa				7	17.5
Total placenta previa		6			
Partial placenta previa		1			
Special x-ray techniques employed				27	
Air cystograms taken	17				
Standing laterals	10				
Erroneous diagnosis				0	100.0
Over-all accuracy of placentography all types			196:200		98.0

Unengaged Presenting Part.—In 50 cases (30 per cent) either abnormal presentation or an unengaged presenting part were found at the time of admission. Minor episodes of bleeding that are associated with an abnormal presentation or unengaged presenting part warrant study to rule out placenta previa. The primigravida at term with an unexplained floating presenting part should have a standing lateral film taken for soft-tissue study along with pelvimetry.

Double Setup Sterile Vaginal Examination.—Sterile vaginal examination in the operating suite with the patient prepared for possible abdominal delivery was employed 44 times with one error, an accuracy of 97.8 per cent. In the face of heavy blood loss and labor, vaginal examination is only a time-consuming and aggravating procedure to a patient in shock. X-ray, the amount and nature of the bleeding, and determination of presentation and engagement are all equally reliable indications for surgical intervention. Vaginal examination is reserved for: (1) equivocal cases near term without bleeding, (2) cases of total placenta previa near term diagnosed only by x-ray and not bleeding, and (3) suspected cases of low lying posterior placenta previa. There were no repeat vaginal examinations done in this series.

Supportive Management.—A total of 263 units of blood were given, averaging 1.6 units per patient; 41 of 43 patients with total placenta previa were transfused (97.5 per cent) with 139 units (3.23 per patient); 34 of 56 patients with partial placenta previa were transfused (60.7 per cent) with 81 units (1.45 per patient); 7 of 13 with low lying posterior placenta previa were transfused (61.5 per cent) with 17 units (1.3 per patient); and 17 of 54 with low lying placenta previa were transfused (31.5 per cent) with 26 units (0.48 per patient). There is a close parallel between partial placenta previa and low lying posterior placenta previa in blood requirements to cover losses. This is illustrated in Fig. 1.

Methods of Delivery.—The methods of delivering the 169 infants are shown in Table VI. The 3 low lying placenta previas encountered at repeat cesarean section were unsuspected prior to operation. One Porro cesarean section was done for severe amnionitis in a case of total placenta previa. One hysterectomy was performed after cesarean section for focal placenta accreta complicating total placenta previa. The patient bled from the lower uterine segment postoperatively necessitating 9,000 ml. blood replacement before and during emergency operation. A second postcesarean section hysterectomy was done on a 40-year-old grand multipara found to have recurrent total placenta previa in successive pregnancies as well as two previous cesarean sections.

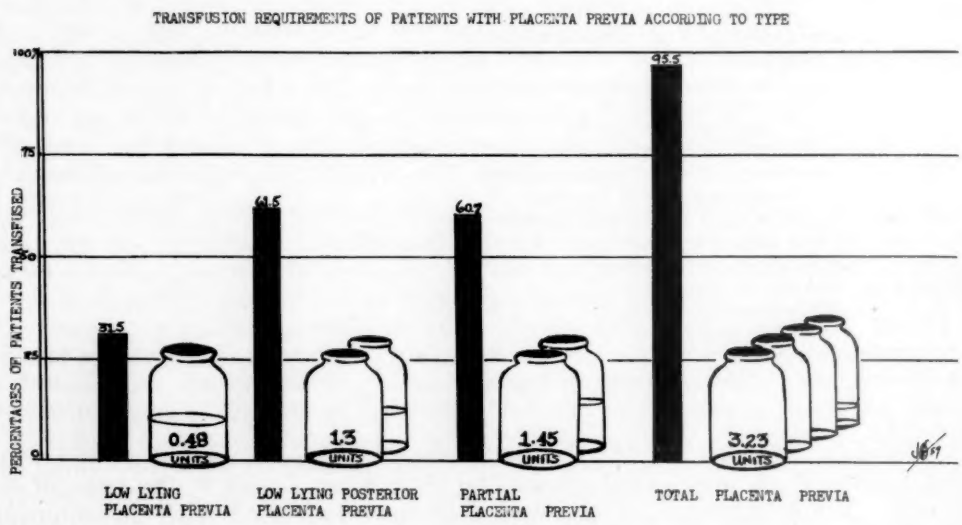

Fig. 1.

TABLE VI. METHODS OF DELIVERY IN 166 CASES OF PLACENTA PREVIA AT THE U. S. NAVAL HOSPITAL, PORTSMOUTH, VIRGINIA

METHOD OF DELIVERY	NO. CASES	%	TOTAL	PARTIAL	LOW LYING	LOW LYING POSTERIOR
1. Spontaneous	53	34.1	0	24	26	3
2. Low forceps	33	19.5	1	10	19	3
3. Midforceps	7	4.1	0	1	6	0
4. Breech extraction or assist	13	7.7	1	9	3	0
5. Version and extraction	2	1.1	0	2	0	0
6. Transverse low cervical cesarean section	61	36.1	41	10	3	7
7. Porro hysterectomy	1	0.6	1	0	0	0
8. Hysterectomy post cesarean section	2	1.1	2	0	0	0

Complications.—The complications associated with placenta previa in this series are listed in Table VII. Premature rupture of the membranes and subsequent amnionitis proved quite disastrous from a fetal standpoint. Rupture of the membranes accompanied by bleeding from placenta previa offers an excellent culture medium for bacterial growth and the amnionitis is usually severe.

TABLE VII. MEDICAL, SURGICAL, AND OBSTETRICAL COMPLICATIONS ASSOCIATED WITH PLACENTA PREVIA

Antepartum.—	
Amnionitis	4
Diabetes mellitus, Class D	1
Epilepsy (grand mal)	1
Fibromyomas of the uterus (8 cm.)	1
Hepatomegaly, splenomegaly (etiology?)	1
Hypertension	1
Pneumonia, lobar, bilateral	1
Polyhydramnios	2
Pre-eclampsia	8
Pyelitis	6
Rheumatic heart disease, Grade II	1
Ureteral calculus	1
Intrapartum.—	
Contraction ring, lower uterine segment	1
Focal placenta accreta	1
Prolapse of the cord	7
Retained or adherent placenta	4
Postpartum.—	
Cerebral venous thrombosis	1
Endometritis	3
Peritonitis, postoperative (cesarean section and hysterectomy)	1
Wound dehiscence (cesarean section)	1

Intra partum, there was a 4.2 per cent incidence of prolapse of the cord, which resulted in 2 stillbirths and 2 neonatal deaths. Abnormal presentations and unengaged presenting parts were responsible for the increased incidence. There were also 4 cases of retained placenta and one of focal placenta accreta that was discussed earlier.

The postpartum complications were limited to infection in the form of endometritis or peritonitis depending upon the route of the delivery. One wound dehiscence occurred in a case of total placenta previa that had been complicated ante partum by resistant pyelitis.

Anesthesia.—Anesthesia for the vaginal deliveries was chiefly conduction in type. Spinal (saddle block) was employed to deliver the primigravida who was stabilized and not actively bleeding in the second stage of labor. Pudendal block was the anesthesia of choice for the delivery of the multipara or the primigravida with minimal bleeding in whom a hypotensive reaction could not be risked. Cesarean sections were performed under spinal anesthesia when bleeding was minimal or absent, and under local (Xylocaine 0.5-1.0 per cent) when fetal distress, bleeding, or shock was the indication. There were 7 operative procedures carried out under cyclopropane anesthesia with only 3 infant survivals; this high fetal mortality rate (57 per cent) is similar to that reported by Hibbard[11] (30.3 per cent).

Results

In 66.2 per cent of the patients labor was so well established that they failed to stop bleeding, anoxia and shock threatened the fetus and mother, and delivery was accomplished within 12 hours after admission. An additional 5.4 per cent of the patients either continued to bleed or had a short latent period followed by labor and more bleeding and were delivered within 24 hours after

admission. Thus, as a result of labor and/or bleeding, 71.6 per cent of the patients were delivered on the day of admission, leaving only 28.4 per cent who could be managed conservatively. Only 22.3 per cent gained one additional week or more of gestational development for their infants, since 6 per cent were delivered before the seventh hospital day.

In this conservative group, 19 of the patients were admitted before the thirty-second week and 18 before the thirty-sixth week of gestation. Only 5 of their infants weighed less than 1,500 grams and 22 (60 per cent) weighed over 2,500 grams at birth. There were 1,192 additional hospital days before delivery, an average of 32.2 days per patient. The quantity of blood given, 39,500 ml., or 2.13 units per patient, was 20 per cent less than that required to support the patients who were bleeding actively at the time of admission and delivery. Of interest is the fact that in the group treated expectantly there were 20 per cent more total placenta previas than in the general study (25.9 versus 45.9 per cent).

Seventy-two of the 110 deliveries which occurred in the first 24 hours produced mature infants, with only 2 perinatal deaths, neither of which was caused by early delivery. Labor and/or bleeding necessitated the delivery of 27 premature and 11 immature infants within the first 12 hours following admission, and 6 more premature and 2 immature infants were delivered within 24 hours following admission.

Fetal survival with conservative management was 89.1 per cent, which is 5 per cent better than our experience in the entire study. When one recalls that 52 per cent of the infants in the entire study were mature by gestational age at the time of admission as compared to only 8 per cent of the conservative group, the merit of this attack on prematurity and associated fetal losses in the management of placenta previa is self-evident.

The maternal mortality rate was zero and the uncorrected fetal mortality rate was 15.9 per cent. There were 3 infants with congenital anomalies incompatible with life, a corrected fetal mortality of 14.1 per cent (Table VIII).

TABLE VIII. MATERNAL AND FETAL MORTALITY ASSOCIATED WITH PLACENTA PREVIA

AUTHOR	YEARS	CASES	MATERNAL (%)	FETAL (%)	
Beilly[2]		162			
	1940-1946		1.23	28.2	
	1946-1950		0.0	9.8	
Davidson[3]	(1957)	137	0.0	13.0	
Eadie and Randall[4]	(1954)	131	2.3	43.2	uncorrected
Grant, F. G.[9]		201	0.0	11.9	
Hatten, Kirkpatrick, and Thornton[10]	(1947-1954)	56	0.0	26.2	uncorrected
Johnson[14]	(1939-1950)	201	0.0	21.0	
Macafee[16] (2 series)					
Conservative treatment		1,000 plus	5.9	54.0	
Immediate treatment		1,000 plus	7.0	59.0	
Macafee (personal series)	(1937-1944)	177	0.57	23.5	
Schmitz[20]	(1941-1951)	112	0.89	22.3	
Semmens, U. S. Naval Hospital, Portsmouth, Virginia	(1954-1957)	166	0.0	15.9	uncorrected
				14.1	corrected

Comment

We were prompted to undertake this study of the conservative management of placenta previa because: (1) a reduced incidence of premature deliveries offered the best means of improving fetal salvage, and (2) temporization permitted more accurate diagnosis and a much better prognosis for the mother in her current as well as her future pregnancies.

We feel that any bleeding before and during labor deserves a concerted effort to make a positive diagnosis; and if placenta previa is found to be present, no matter what the circumstances, all the benefits of hospital management must be afforded to the mother and her unborn infant. Delivery of a viable infant and replacement of maternal blood loss do not excuse the obstetrician from making a positive diagnosis, and the indiscriminate use of terms such as "marginal sinus rupture" to classify cases that border between abruptio placentae and placenta previa should be discouraged.

The younger average age of patients (24.5 years) suggests that placenta previa need not be a complication of the older multipara. Repeated pregnancies in a short time interval are probably equally responsible for the uterine changes that predispose a patient to an abnormal placental implantation.

There were 3 patients who had had placenta previa in a previous pregnancy. One had total placenta previa in 2 successive pregnancies. Johnson reports 2 recurrences of placenta previa among 120 patients.

The clinical significance of abnormal presentation is evident with 35 times as many transverse lies and 3 times as many breech presentations with placenta previa. The 4.2 per cent incidence of prolapse of the cord is an anticipated consequence of the large percentage of unengaged presenting parts (60 per cent) at the time of labor and delivery. There were 56 transverse lies in 16,532 deliveries (0.34 per cent) during the years 1954 to 1956, inclusive, and 19 (34 per cent) were associated with placenta previa. Anteroposterior and soft-tissue lateral x-ray for fetal position and placental localization at the same time makes good sense in the evaluation of the patient suspected of having a transverse lie.

Bleeding *is evidence of labor* in placenta previa, since it is brought about by retraction of the lower uterine segment from the placenta during dilatation of the cervix. Increasing bleeding and evidence of uterine contractions call for prompt delivery. Bleeding in excess of 500 ml. in a single episode seldom abates, and if it is allowed to continue and exceed 1,000 ml. before delivery, the fetal mortality rate doubles.

Excessive x-ray exposure of the fetus should be avoided and the single standing soft-tissue lateral film has been the most effective method of screening suspected cases. Fifteen per cent of the cases x-rayed were positively diagnosed in this manner. A selective filtration technique such as that described by Reeves and Cahoon[17] offers the best visualization of the placenta and uterus on lateral view.

In a review of approximately 5,000 cases of placenta previa reported in the literature,[4, 5, 14, 20] the incidence of total placenta previa is 26 per cent. We feel that a cesarean section rate more than 15 per cent above the percentage of total placenta previas reflects an easy but not always sound solution to this problem. Surgical procedures on the gravid uterus leave weaker scars, especially if the incision is in the placental site. The only valid indications for abdominal delivery in placenta previa other than total are: abnormal presentations, low lying posterior placentas that prevent engagement, and the occasional partial placenta previa in the primigravida and certain multiparas who continue to bleed.

The problem of anesthesia, especially in the presence of shock or near shock, is extremely difficult. One is barely able to transfuse these patients rapidly enough to offer the circulatory support necessary to effect an emergency abdominal delivery. Regional or local anesthesia offers a greater margin of safety for the mother and her baby. It has been pointed out that there was no fetal loss in 7 cesarean sections done under local anesthesia for total placenta previa with excessive bleeding; whereas we experienced a 50

per cent fetal loss in a comparable group delivered under cyclopropane anesthesia. Two of the infants subjected to autopsy showed hemorrhagic changes in the lungs and pneumonia.

Summary

One hundred sixty-six cases of placenta previa in 18,408 deliveries at the U. S. Naval Hospital, Portsmouth, Virginia, are presented and reviewed. The management is discussed in detail. Diagnostic aids, including x-ray and selective filtration techniques, and sterile vaginal examination are appraised for accuracy as well as hazard to the patient. Methods of delivery are discussed, including specific indications for abdominal delivery. Section rates more than 15 per cent above the number of total placenta previas are felt to represent an easy but unwise solution for bleeding problems. Major complications associated with placenta previa and abnormal presentations are mentioned, and the choice of anesthesia for abdominal as well as vaginal delivery, especially in the face of circulatory instability, is discussed.

An additional month or more of continued intrauterine gestation for the infants was averaged in 22.3 per cent of cases; 88 per cent of the fetuses in this group were immature or premature by gestational age at the time of admission; 60 per cent of the infants weighed over 2,500 grams at the time of delivery, and an over-all fetal survival rate of 89.1 per cent was credited to this group of patients. Despite there being almost twice the number of total placenta previas in this group, the actual blood needs were 20 per cent less than among patients who were in active labor and bleeding at the time of admission.

For an additional 11.5 per cent of the patients temporization permitted more accuracy in the diagnosis of the type of placenta previa present and the selection of a method of delivery which offered the infant and mother the best prognosis in the current pregnancy as well as in future pregnancies.

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References

1. Bartholomew, R. A., and others: Obst. & Gynec. **1:** 41, 1953.
2. Beilly, J. S., Greenberg, M. M., Aaron, J. B., and Peck, S. J.: Am. J. Obst. & Gynec. **63:** 414, 1952.
3. Davidson, V. A., and Brunken, R.: J. Internat. Coll. Surgeons **27:** 466, 1957.
4. Eadie, F. S., and Randall, J. H.: Obst. & Gynec. **3:** 11, 1954.
5. Eastman, N. J.: Williams Obstetrics, ed. 11, New York, 1956, Appleton-Century-Crofts, Inc.
6. Falls, F. H.: S. Clin. North America **33:** 17, 1953.
7. Fish, J. S., and others: South. M. J. **47:** 954, 1954.
8. Fitzgerald, J. E., Webster, A., Geittmann, W. F., and Zummo, B.: Am. J. Obst. & Gynec. **68:** 659, 1954.
9. Grant, F. G.: J. Obst. & Gynaec. Brit. Emp. **62:** 497, 1955.
10. Hatten, J. Q., Kirkpatrick, S. A., and Thornton, W. N., Jr.: Am. J. Obst. & Gynec. **70:** 1181, 1955.
11. Hibbard, L. T.: Obst. & Gynec. **8:** 613, 1956.
12. James, D. W., and Misch, K. A.: J. Obst. & Gynaec. Brit. Emp. **62:** 551, 1955.
13. Johnson, H. W.: Am. J. Obst. & Gynec. **50:** 248, 1945.
14. Johnson, H. W.: Am. J. Obst. & Gynec. **59:** 1236, 1950.
15. Macafee, C. H. G.: Postgrad. M. J. **25:** 297, 1949.

16. Macafee, C. H. G.: J. Obst. & Gynaec. Brit. Emp. **52**: 313, 1945.
17. Reeves, R. J., and Cahoon, J. B.: M. Radiog. & Photog. **28**: 2, 1952.
18. Russell, J. K.: Lancet **269**: 322, 1955.
19. Russell, J. K., and Warrick, C. K.: Lancet **268**: 785, 1955.
20. Schmitz, H. E., O'Dea, N. J., and Isaacs, J. H.: Obst. & Gynec. **3**: 3, 1954.
21. Stallworthy, J.: AM. J. OBST. & GYNEC. **61**: 720, 1951.
22. Watson, H. G.: West. J. Surg. **63**: 151, 1955.
23. Weinberg, A., Rizzi, J., McManus, R., and Rivera, J.: Obst. & Gynec. **8**: 396, 1956.
24. Weinberg, A., and Deckoff, S.: Obst. & Gynec. **10**: 146, 1957.

ANEMIA IN OBSTETRICS AND GYNECOLOGY: AN EVALUATION OF THERAPY WITH PARENTERAL IRON*†

JACK A. PRITCHARD, M.D., DALLAS, TEXAS

(From the Department of Obstetrics and Gynecology of the University of Texas Southwestern Medical School)

THE problem of anemia in obstetrics and gynecology is formidable. In an attempt to cope with this problem it appears that not infrequently the obstetrician-gynecologist has armed himself with little more than some form of hemoglobinometer and the wares of the blood bank. The dangers associated with a lowered hemoglobin concentration apparently have been considered greater than those inherent in failure to establish and treat the cause of the anemia and those associated with blood transfusion therapy.

This report results from a continuing study of anemia in obstetric and gynecologic patients and summarizes several observations made to date. It deals particularly with the use of parenteral iron in these patients.

Methods

Standard laboratory methods as outlined in *A Syllabus of Laboratory Examinations in Clinical Diagnosis*[1] have been used. Measurements of total hemoglobin mass were made as follows:

Twenty to thirty milliliters of blood was obtained by venipuncture and injected into ACD solution to which had been very recently added 100 to 200 μc of radioactive chromium as sodium chromate. After incubation for 20 to 30 minutes at room temperature the red cells were washed twice with about 50 ml. of sterile saline. Then enough sterile saline was added to the labeled cells to make the final volume about 50 ml. After thorough mixing a 20 ml. routine laboratory syringe was filled exactly to the 20 ml. mark through a 20 gauge needle. The labeled red cells were then injected intravenously. The syringe and needle were again filled in exactly the same manner and the red cell suspension was placed in a volumetric flask with enough distilled water to make exactly 2,000 ml.

Blood was drawn from the patient one-half to one hour after injection. Its hemoglobin concentration and packed cell volume were measured in duplicate. The radioactivity of 4.0 ml. of blood previously frozen and thawed and of 4.0 ml. of the standard red cell-water mixture was measured in a well-type scintillation counter. The total circulating hemoglobin was calculated as follows:

$$\text{Blood volume} = \frac{2{,}000 \times \text{radioactivity of standard}}{\text{Radioactivity of subject's blood}}$$

$$\text{Total hemoglobin} = \frac{\text{Blood volume} \times \text{hemoglobin concentration (Gm./100 ml.)}}{100}$$

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The Usual Causes of Anemia in Obstetrics and Gynecology

Acute or chronic blood loss has been by far the major cause of anemia in patients seen on the gynecologic service. Concomitant with the loss of 100 ml. of blood with a hemoglobin level of 14 Gm./100 ml. is the loss of nearly 50 mg. of iron. To replenish hemoglobin so lost, to maintain iron stores, and to correct any pre-existing deficits in iron stores in the case of chronic blood loss or of previous numerous pregnancies, it is mandatory that medicinal iron be given. Therapy in typical cases will be considered subsequently.

It is well documented that there is considerable need for extra iron during pregnancy (Fig. 1). Normally pregnancy will result in a decrease in maternal iron stores of at least 500 mg. due to transfer of iron to the fetus and placenta and in blood lost at delivery unless a similar amount of iron is obtained from exogenous sources. As the plasma volume expands during pregnancy another 500 mg. of iron must be utilized for hemoglobin synthesis or the hemoglobin concentration will fall appreciably. Excessive blood loss associated with delivery, of course, also dissipates maternal iron proportionately to the amount of hemorrhage. Unless iron has been supplied to such a patient it is apparent that eventually, and especially during a subsequent pregnancy, a marked impairment in the synthesis of hemoglobin may ultimately result.

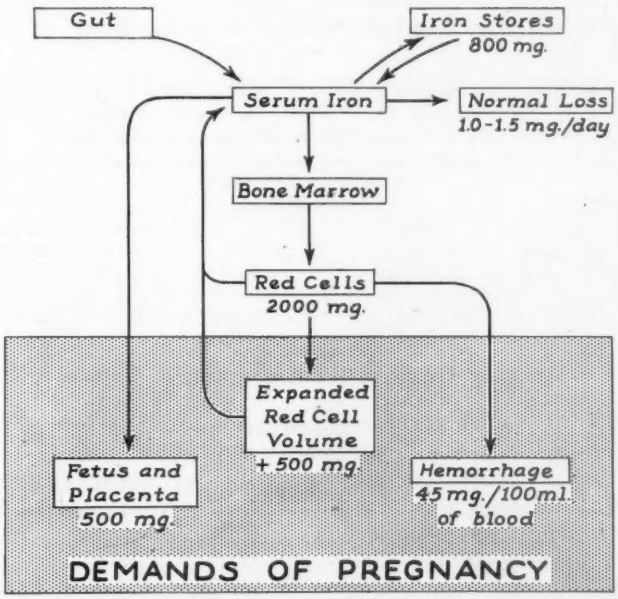

Fig. 1.—Outlined in the upper portion are the pathways for iron absorption, transport, utilization, and loss. Shown below are the factors which cause the marked increase in demands for iron during gestation.

During the past 2 years a hematologic survey was carried out on nearly all of the obstetric patients seen at Parkland Memorial Hospital with reduced levels of hemoglobin. During this time there were 9,180 deliveries; the great majority of the patients were indigent and Negro. It soon became apparent that the anemia was due to hemorrhage, pre-existing iron deficiency, or both in a great majority of patients. The exceptions noted were 2 cases of sickle-cell anemia, 3 of sickle-hemoglobin C disease, 2 of homozygous hemoglobin C disease, 2 cases of megaloblastic anemia of pregnancy, several cases of

anemia associated with chronic renal disease, several associated with infections, and a few apparently due to drug sensitivity, the drug usually being phenacetin.

Pseudoanemia resulting from hospital laboratory error was not uncommon. To determine the magnitude of the problem of error in a hospital service laboratory the following studies were carried out: In 100 obstetric patients when attending prenatal clinic for the first time and again on the second or third postpartum day the hemoglobin levels were measured by one of the hospital service laboratories in a photometer using 0.02 ml. of blood. The same morning blood was also obtained through a venipuncture by the departmental research laboratory and its hemoglobin content was measured in duplicate in a frequently standardized Beckman Model B spectrophotometer; 0.1 to 0.2 ml. of blood was used for the determination. As shown in Table I, the average hemoglobin levels reported by the regular laboratories were 9.5 Gm. per 100 ml. initially and 10.9 Gm. per 100 ml. finally. At the same times, according to the departmental research laboratory, the mean hemoglobin levels were 11.0 Gm. per 100 ml. and 12.4 Gm. per 100 ml. The greatest individual difference for any patient was 8.0 Gm. per 100 ml. reported by the clinic laboratory and 12.8 Gm. per 100 ml. found by the research laboratory. Whereas 12 per cent of the patients initially were found to have a hemoglobin level below 10.0 Gm. per 100 ml. when the determination was carried out by the research laboratory, according to the clinic laboratory 76 per cent had a hemoglobin level below 10.0 Gm. per 100 ml.

TABLE I. A COMPARISON OF THE HEMOGLOBIN LEVELS (GM./100 ML.) IN 100 OBSTETRIC PATIENTS WHEN MEASURED BY THE CLINIC OR HOSPITAL SERVICE LABORATORIES AND BY THE DEPARTMENTAL RESEARCH LABORATORY*

	INITIAL	RANGE	NO. PATIENTS WITH < 10.0 GM.	POSTPARTUM	RANGE	NO. PATIENTS WITH < 10.0 GM.
Service laboratory	9.5	7.0-12.5	76	10.9	8.0-13.4	30
Research laboratory	11.0	8.5-12.8	12	12.4	9.3-15.5	10

*Half of the patients in this study received no iron medication during pregnancy.

Anemia During the Antepartum Period

Theoretically the relatively large requirements for iron during pregnancy can be met either by utilizing iron made available by oral or parenteral administration or by utilizing stored iron if iron stores are sufficient. A study was carried out in indigent clinic patients to determine whether the frequency of failure of self-administration of oral iron, or, less likely, faulty absorption was a problem of sufficient magnitude to warrant the routine parenteral administration of iron during the antepartum period.

It was observed that the administration of iron to such pregnant patients was followed by appreciable hematologic improvement, but that the degree of improvement was not significantly better when iron was given intramuscularly as iron-dextran* in a dose of 1,000 mg. rather than dispensed as tablets of ferrous gluconate to be taken daily in a dose of 1.0 Gm. a day. When no iron was given, the average hemoglobin level at the end of pregnancy was 11.3 Gm. per 100 ml., whereas when iron was given either intramuscularly or orally the predelivery mean hemoglobin concentration was 12.5 Gm. per 100 ml. Of considerable importance, when no iron was given, 16 per cent of the patients came to delivery with a hemoglobin level below 10.0 Gm. per 100 ml.,

*Supplied as Imferon by Lakeside Laboratories, Milwaukee, Wis.

but when iron was given either orally or intramuscularly no patient had a hemoglobin concentration below 10.0 Gm. per 100 ml. Patients in the middle trimester of pregnancy with a hemoglobin level as low as 8.1 Gm. per 100 ml. showed a satisfactory response when given oral iron. In fact in 9 such patients with a hemoglobin level ranging from 8.1 to 9.9 Gm. per 100 ml. and averaging 9.1 Gm. per 100 ml. the hemoglobin level at the end of pregnancy 6 to 19 weeks later ranged from 10.3 to 13.4 Gm. per 100 ml. and averaged 12.1 Gm. per 100 ml. It should be pointed out that the patients given oral iron were closely observed and urged repeatedly to take the medication over an average interval of 12 weeks.

It was concluded that iron supplementation was of considerable value during pregnancy but that the routine use of the intramuscular route to supply the iron requirements of pregnancy was not justified. This study has been reported in detail elsewhere.[2]

Nonetheless there is a very real place for iron-dextran in obstetrics. The iron-deficient anemic patient who either refuses or obviously forgets to take iron orally can be safely and easily supplied with iron by intramuscular injection. The gastrointestinal tract appears to be more easily upset during pregnancy; consequently oral iron is not always well tolerated. Analysis of a group of private patients cared for during the past 2½ years showed that 20 per cent of them would not take one or more oral iron preparations during pregnancy because of gastrointestinal disturbances. In the occasional multiparous patient in whom the hemoglobin level dropped to 10.0 Gm. per 100 ml. or less, and in whom no other cause for anemia was found, iron has been given intramuscularly with subsequent hematologic improvement.

TABLE II. THE RESPONSE TO INTRAMUSCULAR IRON IN A PATIENT PREGNANT FOR THE ELEVENTH TIME WHO BLED FROM A RUPTURED LEG VARIX 3 WEEKS PRIOR TO THERAPY

DAYS AFTER THERAPY	HEMOGLOBIN CONCENTRATION (GM./100 ML.)	INCREASE (GM./100 ML.)	BLOOD VOLUME (ML.)	HEMOGLOBIN MASS (GM.)	INCREASE (GM.)
0	5.8	—	5010	316	—
15	9.3	+3.5	5570	517	+201
30	10.6	+4.8	5700	604	+288
39	11.5	+5.7	—	—	—
42*	13.4	+7.6	4650	622	+306

Mg. Fe utilized for hemoglobin synthesis = 306 × 3.4 = 1040 mg.

Theoretically available for fetus and iron stores = 2,000 - 1,040 = 960 mg. Fe.

Probably actually available for fetus and iron stores = 2,000 × 4/3 - 1,040 = 460 mg. Fe.

*Three days post partum.

Iron-dextran proved especially valuable in treating the severely anemic iron-deficient patient who was approaching term. By supplying the iron intramuscularly rather than orally at no time was hemoglobin production limited by the availability of iron. Therefore the deficit was corrected as rapidly as possible. The results of therapy in such a patient are shown in Table II. In this patient of great parity and, no doubt, with depleted iron stores, the hemoglobin level rose from 5.8 Gm. to 9.3 Gm. per 100 ml. in 15 days. Hemoglobin equivalent to that in 3 pints of blood was made during this time. Just prior to labor 39 days after the start of therapy the hemoglobin level had doubled to reach 11.5 Gm. per 100 ml. Calculations shown in Table II and discussed subsequently indicate that the 2,000 mg. of iron given was not enough to replenish fully the iron stores in this patient so 500 mg. more was given post partum.

Anemia Following Obstetric Hemorrhage

Patients in this group had hemorrhaged as the result of one or more of the following conditions: abortion, ruptured ectopic pregnancy, uterine atony, placenta previa, ruptured uterus, and abruptio placentae with or without hypofibrinogenemia. In the cases where blood transfusions were used the volume of blood administered was limited to enough to combat any signs or symptoms of shock. After any evidence of shock had been combated and the bleeding had been arrested, further transfusion therapy was withheld regardless of the hemoglobin level except in the infrequent situation where another surgical procedure was to be performed or where there was infection, cardiac disease, or in the surprisingly uncommon case where ambulation resulted in evidence of vasomotor instability. Instead, iron-dextran was administered intramuscularly. The subsequent increase in the concentration of circulating hemoglobin was observed at one to 2 week intervals during the next 6 weeks.

Observations made in 21 such severely anemic patients who received from 1,250 to 2,000 mg. of iron intramuscularly are summarized in Table III. The hemoglobin levels on the third to the fifth postpartum day averaged 6.7 Gm. per 100 ml. and ranged from 5.5 to 7.9 Gm. per 100 ml. Three weeks later (either actually measured or determined by interpolation from the levels measured at the second and the fourth week) the hemoglobin level averaged 11.6 Gm. per 100 ml., an increase of 3.9 Gm. per 100 ml., and ranged from 9.8 to 12.3 Gm. per 100 ml. The increase of 3.9 Gm. per 100 ml. in 3 weeks is identical to that observed by Scott.[3] By the sixth week it had reached an average concentration of 13.2 Gm. per 100 ml., a mean increase of 6.5 Gm. per 100 ml., and ranged from 11.8 to 14.9 Gm. per 100 ml.

TABLE III. HEMOGLOBIN LEVELS (GM./100 ML.) BEFORE AND AFTER THERAPY WITH IRON-DEXTRAN IN 21 SEVERELY ANEMIC PATIENTS FOLLOWING ACUTE BLOOD LOSS IN PREGNANCY

	3 TO 5 DAYS POST PARTUM	3 WEEKS POST PARTUM	INCREASE	6 WEEKS POST PARTUM	INCREASE
Average	6.7	11.6	4.9	13.2	6.5
Range	5.5-7.9	9.8-12.3	3.0-6.2	11.8-14.9	4.5-8.5

It is probable that most of these patients would have shown a similar response if oral iron had been prescribed and had been taken faithfully for a sufficiently long period of time. In actual practice, however, it has been quite difficult to convince many women, once pregnancy has been completed, to continue to take this medication. Therefore, the major advantage offered by the intramuscular route in such severely anemic women is one of security. The amount of iron needed for hemoglobin regeneration can be calculated and readily given to the patient. The hemoglobin deficit is rapidly repaired without depleting iron stores and without the likelihood of an adverse reaction.

Anemia Due to Chronic Blood Loss From Excessive Menstrual Flow

Not infrequently encountered on most gynecologic services is the patient with appreciable anemia associated with menstrual periods characterized by a marked increase in the amount of menstrual flow but without a remarkable prolongation of duration of flow. In such patients the standard procedure has been to admit them to the hospital, promptly correct their hemoglobin deficits with several blood transfusions, and then operate.

Since such patients are markedly iron deficient with exhausted iron stores as the result of the chronic intermittent blood loss and since the amount of

iron absorbed from the usual diet is negligible compared to the actual amount needed for effective hemoglobin synthesis, it is impossible without specific iron therapy for these patients to correct their anemia during the interval of 3 weeks or so between menstrual periods. Rather than follow the nearly universal procedure of using blood transfusions and operation as outlined above, it was elected in such cases to give by intramuscular injection 1,500 to 2,000 mg. of iron as iron-dextran, a dose calculated to supply enough iron to allow repair of the deficit in circulating hemoglobin at a maximal rate, and then to observe the response during the next 3 weeks. Observations made in 8 representative patients are summarized in Table IV.

TABLE IV. INCREASE IN HEMOGLOBIN CONCENTRATION (GM./100 ML.) AFTER INTRAMUSCULAR IRON-DEXTRAN IN PATIENTS WITH CHRONIC HYPERMENORRHEA

CASE DIAGNOSIS	FE INJECTED (MG.)	INITIAL	7 DAYS	14 DAYS	21 DAYS	INCREASE
1 Myomas	500/day × 4	6.0	7.6	9.1	10.9	4.6
2 Myomas	500/week × 3	7.3	8.9	9.7*	11.2	3.9
3 Myomas	500/day × 3	7.3	9.1	—	11.1*	3.8
4 Myomas	500/week × 3	7.3	9.2	10.5	11.6	4.2
5 Hyperplasia	500/week × 3	7.6	9.8	10.6*	12.2	4.6
6 Hyperplasia	500/week × 3	7.6	9.5	10.5*	11.6	4.0
7 Myomas	500/week × 3	7.9	10.2	—	12.2	4.3
8 Hyperplasia	500/week × 3	8.5	10.0	11.3	12.3	3.8
Average		7.4	9.3	10.4	11.6	4.2

*Menstruating.

The initial hemoglobin level ranged from 6.0 Gm. to 8.5 Gm. per 100 ml. and averaged 7.4 Gm. per 100 ml. One, 2, and 3 weeks later it averaged 9.3 Gm., 10.4 Gm., and 11.6 Gm. per 100 ml., respectively. The hemoglobin concentration at the end of the 3 week period ranged from 10.9 to 12.3 Gm. per 100 ml.

In 3 instances (Cases 1, 2, and 6) the total circulating hemoglobin was measured at the beginning and end of this period. The increases in hemoglobin mass were 225 Gm., 191 Gm., and 222 Gm., respectively. These patients during 3 weeks manufactured hemoglobin equivalent to that in 3 pints of normal donor blood since one pint of donor blood contains about 70 Gm. of hemoglobin.

Both the rapid increase in the hemoglobin concentration and the prompt increase in feeling of well-being noted by the patients were gratifying in all instances. Operation was carried out in 7 of the 8 patients; no transfusions were given. In one instance operation was not performed.

CASE 5.—J. S. a 30-year-old unmarried white woman, had noted heavy menstrual flow for about 8 years. Frequently she was forced to go to bed when menstruating because of marked weakness as well as the amount of flow. She had been previously admitted to a hospital for blood transfusions and uterine curettage. Marked anemia and hyperplasia of the endometrium were diagnosed.

The patient refused to take iron orally because of vomiting, gastrointestinal cramping, and diarrhea. She was treated at considerable expense and without apparent effect with injections of liver extract, folic acid, vitamin B_{12}, progesterone, estrogens, and testosterone. Both the hypermenorrhea and the weakness persisted. The patient continued to work as a receptionist in a doctor's office.

Physical findings were limited to pallor. The hemoglobin level was 7.6 Gm. per 100 ml., the hematocrit was 28, and a stained smear of the peripheral blood showed hypochromia. The platelets were normal. Iron deficiency anemia due to chronic hypermenorrhea was diagnosed.

Therapy consisted of 500 mg. of iron as iron-dextran each week for 3 weeks. At the end of 3 weeks the hemoglobin level had risen to 12.2 Gm. per 100 ml.

The patient has refused uterine curettage. Menstrual flow is still quite heavy but for only one day each month. During the past 3 months the hemoglobin and hematocrit dropped from 12.5 Gm. per 100 ml. and 40 to 11.2 Gm. per 100 ml. and 36, so another 500 mg. of iron as iron-dextran was given. Two weeks later the hemoglobin level was 12.2 Gm. per 100 ml. At this time 500 mg. of iron-dextran was given.

On the basis of calculations to be discussed subseqquently it is apparent that most of the iron absorbed after the initial therapy of 3 weekly injections of 500 mg. each was used to form hemoglobin. The deficit in her undoubtedly depleted iron stores was not corrected until the second series of injections was given. Consequently, when she continued to have excessive blood loss following the initial course of therapy, the hemoglobin level fell since there was no iron which could be mobilized from storage for hemoglobin synthesis. This patient will be followed at intervals of 3 months.

Other cases in this group are worthy of brief comment. In Case 3 the patient had personally been observed to work rather hard doing housework for 2½ years without volunteering any symptoms suggesting anemia. When first examined because of large myomas the hemoglobin level was found to be only 7.3 Gm. per 100 ml. Three weeks later the hemoglobin level was 11.1 Gm. per 100 ml.; hysterectomy was performed without blood transfusions. Case 8 is that of a 30-year-old patient who, prior to tubal ligation 2 years before, had produced 13 children including 2 sets of twins during which time she had been transfused 14 times. There was laboratory evidence of marked iron deficiency. Her anemia was rapidly corrected after therapy with iron-dextran.

Again it appears definitely advantageous for these patients to repair the deficits in circulating hemoglobin as rapidly as possible so that the indicated surgical procedures could be safely performed. Giving iron intramuscularly assured the constant availability of iron for hemoglobin synthesis at a maximal rate. It should be pointed out that most of these patients would show a similar hemoglobin response if oral iron had been prescribed and if it had been faithfully taken each day. Oral iron, however, would probably correct the deficits in iron stores with difficulty. Available evidence indicates that initially most of the iron absorbed from the gut is used for hemoglobin synthesis and that as soon as the deficit in hemoglobin concentration is corrected the stimulus for augmented iron absorption from the gut is lost. Therefore the minimal amount of iron absorbed subsequently would replenish iron stores only at a very slow rate.[4, 5]

Calculation of Dosage and Method of Injection of Iron-Dextran

An attempt was made to determine what fraction of the iron injected intramuscularly as iron-dextran is subsequently utilized for hemoglobin synthesis. Two severely anemic patients with large myomas and chronic hypermenorrhea were judged to be severely iron deficient and to have virtually exhausted their iron stores. In one the initial hemoglobin level was 2.1 Gm. per 100 ml. and in the other it was 4.7 Gm. per 100 ml. The total hemoglobin mass was measured with Cr^{51} labeled red blood cells. Then iron as iron-dextran was given intramuscularly in a daily dose of 250 mg. in each buttock until 2,000 mg. in one case and 1,500 mg. in another had been injected. Fortuitously menses in one case did not recur during the following 35 days prior to operation and in the other it was delayed until 5 weeks after the start of the study. As shown in Table V in one instance 72 per cent and in the other 77 per cent of the injected iron was accounted for in the expanded hemoglobin mass at the time when the hemoglobin mass no longer continued to increase.

TABLE V. MEASUREMENTS OF IRON UTILIZED FOR HEMOGLOBIN SYNTHESIS AFTER INTRAMUSCULAR IRON-DEXTRAN IN CASES OF SEVERE DEFICIENCY DUE TO CHRONIC INTERMITTENT BLOOD LOSS

DAYS AFTER THERAPY	HEMOGLOBIN CONCENTRATION (GM./100 ML.)	INCREASE (GM./100 ML.)	BLOOD VOLUME (ML.)	HEMOGLOBIN MASS (GM.)	INCREASE (GM.)
I. W., myomas, chronic blood loss; 500 mg. Fe I.M. × 4.—					
0	2.1	--	3770	79	--
7	5.8	+3.7	--	--	--
14	8.8	+6.7	4180	368	289
21	10.9	+8.8	4000	437	358
29	12.0	+9.9	4290	515	436
35*	12.2	+10.1	4105	500	421
D. W., myomas, chronic blood loss; 500 mg. Fe I.M. × 3.—					
0	4.7	--	3530	166	--
7	6.4	+1.7	--	--	--
17	8.2	+3.5	4540	372	+206
24	10.0	+5.3	--	--	--
32	11.5	+6.8	4500	518	+352
39†	11.9	+7.2	4225	505	+339

I. W.: Mg. Fe utilized = 421 × 3.4 = 1431

$$\frac{1431 \text{ (utilized)}}{2000 \text{ (injected)}} \times 100 = 72\% \text{ utilization}$$

D. W.: Mg. Fe utilized = 339 × 3.4 = 1153

$$\frac{1153 \text{ (utilized)}}{1500 \text{ (injected)}} \times 100 = 77\% \text{ utilization}$$

*Hysterectomy.
†Menstruating; hysterectomy.

Stevens,[6] using iron-dextran labeled with Fe^{59}, found that 87 per cent of the dose injected intramuscularly was incorporated into circulating hemoglobin. Grimes and Hutt[7] with a similarly labeled preparation noted that 60 per cent of the intramuscular dose was rapidly absorbed but thereafter clearance from the site of injection occurred quite slowly. It is concluded from these several observations that about three fourths of the intramuscularly injected iron can be counted upon to be readily available for hemoglobin synthesis.

The circulating hemoglobin in a nonpregnant woman of average size will contain about 2,000 mg. of iron when the hemoglobin level is 14 to 15 Gm. per 100 ml. Normally iron stores will amount to another 800 mg. of iron. In the case of a previously normal woman of average size with anemia due to acute blood loss, the amount of iron needed for hemoglobin regeneration can be calculated from the following formula:

$$\text{Mg. Fe needed} = 2{,}000 \times \frac{\text{Hemoglobin deficit}}{15}$$

where the hemoglobin deficit equals the ideal of 15 Gm. per 100 ml. minus the actual hemoglobin level.

Since about three fourths of the intramuscularly injected iron seems to be readily utilized for hemoglobin synthesis, the dose to be injected can be calculated as follows:

$$\text{Mg. Fe injected} = \frac{2{,}000 \times \text{hemoglobin deficit}}{15} \times \tfrac{4}{3}$$

or, simplified,

$$\text{Mg. Fe injected} = 180 \times \text{hemoglobin deficit}$$

In the instances where there has been chronic iron deficiency anemia and depletion of iron stores, 800 mg. more of iron is necessary to correct this deficit.

Experience to date indicates that 250 mg. of iron as iron-dextran can be injected into each buttock each day for at least 4 days without undue local reaction. On occasion 500 mg. of iron as iron-dextran have been injected every 8 hours to give 1,500 mg. in 24 hours but with this dosage schedule appreciable local soreness sometimes followed. It should be pointed out that such frequency of injections does not result in an augmentation of the rate of synthesis of hemoglobin. Five hundred milligrams of iron in one week should supply in practically all cases enough iron for maximal synthesis of hemoglobin during that interval. The only reason for more frequent injections would be to supply all of the iron needed to correct the iron deficit prior to the discharge of the patient from the hospital.

Even though anemia in obstetrics and gynecology is very frequently due to acute or chronic blood loss and iron deficiency, it is emphasized that these are not the sole causes of anemia encountered in such patients. Intensive therapy with parenteral iron is to be condemned if there is any doubt as to the actual cause of the anemia. When there is doubt the dose of parenteral iron should be limited to 500 mg. if the patient is not pregnant and to no more than 1,000 mg. if pregnant and the patient should be observed for signs of hematologic response. If the anemia is due only to iron deficiency, within 4 to 5 days the reticulocyte count should rise and within 2 weeks the increase in the concentration of hemoglobin should approach 2.0 Gm. per 100 ml. unless the patient is losing blood or there has been a concomitant marked expansion of the plasma volume due to pregnancy. In the latter instances reticulocytosis would still be found.

It is important to deposit the iron-dextran within muscle since the material is not absorbed from subcutaneous tissue.[8] In subjects who are not obese a 20 gauge needle 1½ inches long has been inserted to the hub and the material then injected. In obese subjects a longer needle has been used. Ambulation enhances the absorption of iron-dextran. The material is transported in lymph away from the site of injection and lymph flow is augmented by exercise and inhibited by pressure over the site of injection.[8] Persistent recumbency should be discouraged.

Adverse Reactions to Parenteral Iron

There has been considerable opportunity to observe any reactions that might follow the injection of iron-dextran intramuscularly. To date more than 6,000 ampules of iron-dextran containing 250 mg. of iron each have been used at Parkland Memorial Hospital by the several clinical services with no definite reactions other than transient soreness at the site of injection and occasional staining of the skin surrounding the site of injection. There have been a few instances of transient moderate fever with or without generalized muscle aching shortly after iron-dextran therapy. To date in such patients when the therapy was repeated under close observation similar reactions have not been detected. Such a lack of serious reactions has also been the experience of Scott and others.[3, 9]

Early in this study 110 obstetric patients were given 600 to 1,000 mg. of iron as iron-dextran with the dosage schedule ranging from 200 mg. a week in alternate buttocks to 250 mg. a week in each buttock. The only reaction noted in any patient was transient local soreness.

In a comparable group of patients the intravenous administration of saccharated iron oxide resulted in a high incidence of reactions. Fifty-five

women in prenatal clinic were given 3 weekly injections of 200 mg. each. A volume of blood equal to the iron solution was drawn into the syringe and the mixture was injected over a period of 5 minutes. One or more of the following reactions were noted one or more times in 31 per cent of these patients: intense pain at the site of injection or along the course of the vein, marked shortness of breath, chest pain, back pain, nausea, and fever.

The lack of veins suitable for injecting iron intravenously was another very real problem encountered in patients who already had been subjected to numerous venipunctures. In these instances iron could be readily given by the intramuscular route. As the result of the high incidence of reactions to intravenous saccharated iron oxide and the difficulty of administration it is now rarely used in obstetric or gynecologic patients at this hospital.

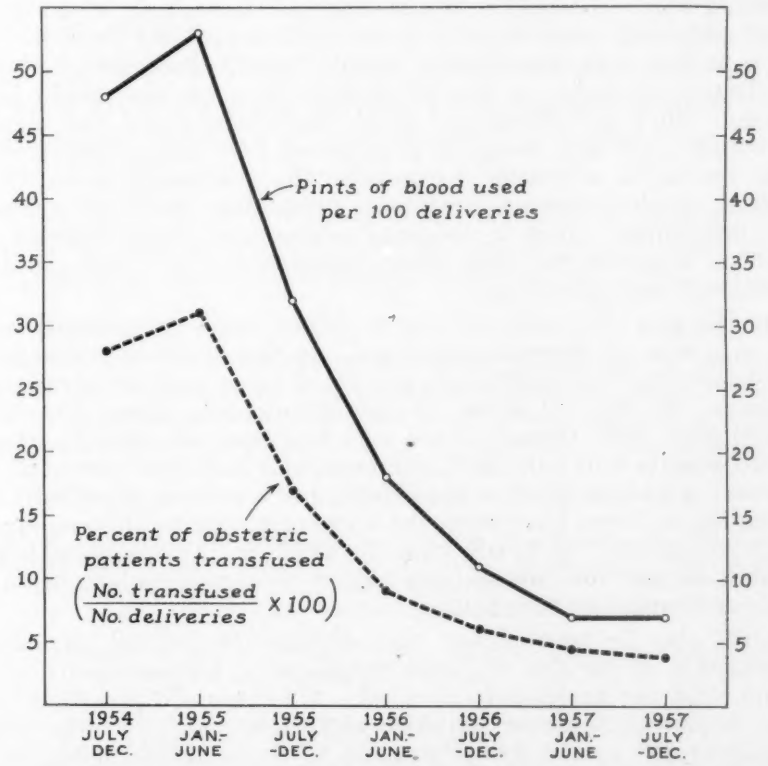

Fig. 2.—Plotted in intervals of 6 months for the year prior to and the 2½ years after starting this study are the number of pints of blood used per 100 deliveries (solid line) and the percentage of obstetric patients transfused (broken line).

The Effect of These Studies on the Use of Blood Transfusions

During the year prior to initiation of these studies the obstetric service at Parkland Memorial Hospital used 1,948 units of blood while 3,867 patients were being delivered. Fifty pints of blood were given for every 100 women delivered; 31 per cent of the obstetric patients received one or more pints of blood. It was felt that transfusion therapy of this magnitude was excessive and that the continuation of such a program would result in unjustified hazards to the patient, excessive cost, depletion of available sources of blood, and, of very considerable importance, such therapy could result in the failure to do more than temporarily correct the underlying defect which caused the anemia.

Since then the use of blood transfusions has dropped markedly (Fig. 2). During the past year 7 pints of blood have been used for every 100 deliveries and only 4 per cent of the obstetric patients have been transfused. If blood had been used at the same rate as in the year prior to the inauguration of this study, a total of 2,403 pints rather than 357 pints would have been used during the past year. This is a reduction of 85 per cent or 2,046 pints per year at the current rate of deliveries.

Eastman[10] similarly has effected a considerable decrease in the amount of blood transfused into pregnant women. For some years they had admitted to the hospital all severely anemic gravidas for one or more blood transfusions. The use of iron-dextran now has practically eliminated these admissions.

It must be emphasized that, even though the amount of blood used has markedly decreased, the requests for blood cross-matched by the blood bank have remained high. Therefore, if the obstetric patient showed any systemic evidence of suffering from blood loss, or if an anesthetic were to be administered to a patient with appreciable anemia, active blood loss, or both, blood was immediately available in the labor-delivery area, and could be rapidly administered. Once all evidence of shock had disappeared, the bleeding had been controlled, and any surgical procedures had been completed, further transfusion therapy was withheld except in the uncommon cases where there was infection, cardiac disease, or where ambulation resulted in evidence of vasomotor instability. Such a program necessitates close observation of all such patients. Patients receiving blood transfusions, however, should receive equal attention from a physician.

During the past 2½ years failure to follow these precautions resulted in one death in a case of abruptio placentae. In this instance compatible whole blood had been obtained early from the blood bank and was available in the delivery room. It was not given by the obstetrician caring for the patient except terminally even though there was a history of massive hemorrhage, both marked anemia and hypofibrinogenemia had been demonstrated, bleeding had not been controlled, shock was evident, and a general anesthetic had been given for the second time to explore the uterus and suture an extensive vaginal and vulvar laceration. It is felt that an error in judgment on the part of the physician caring for this patient rather than any defect in the regime outlined above resulted in this death.

It should also be pointed out that during this period, in spite of the marked reduction in the use of blood transfusions, serious reactions to blood transfusions were not completely avoided. A 17-year-old girl died from post-transfusion homologous serum jaundice and there were 2 nearly fatal transfusion reactions due to the administration of incompatible blood in one and the transfusion of infected blood in the other.

Summary

A survey of the causes for a lowered hemoglobin concentration in obstetric and gynecologic patients indicated that the leading causes were acute blood loss, chronic blood loss, frequent pregnancies with iron depletion, or some combination of these. A not uncommon cause of apparent lowered concentration was error by the service laboratory.

Obstetric patients who received supplementary iron during the antepartum period came to delivery with a higher hemoglobin level than did patients who had received no iron. When the iron requirements of pregnancy were routinely supplied intramuscularly with iron-dextran, the hematologic

improvement was not significantly greater than when ferrous gluconate was given orally. The intramuscular route of administration, however, seemed of considerable value for treating the severely iron-deficient patient to insure maximal response late in pregnancy and subsequently to correct promptly and completely depleted iron stores. While the use of saccharated iron oxide given intravenously was frequently associated with distressing reactions, iron-dextran given intramuscularly produced only transient local soreness.

In gynecologic patients with severe iron deficiency anemia as the result of chronic hypermenorrhea, therapy with iron-dextran resulted in rapid correction of the deficit in circulating hemoglobin so that operation usually could be safely performed at the end of 3 weeks without prior transfusion therapy. Similar prompt hematologic improvement was obtained during the puerperium in patients who were anemic as the result of hemorrhage.

The calculation of dosage and the method of injection of iron-dextran have been discussed, as have been the indications for blood transfusions and for iron replacement therapy.

Since this study was started the use of blood for transfusions but not the amount of blood cross-matched has dropped markedly. In spite of this sharp decrease occasional severe transfusion reactions have not been entirely avoided.

I wish to thank the following for their generous help in this study: Dr. E. E. Muirhead and associates for their frequent hematologic consultations, the obstetric and gynecologic resident staff for their close observation of these patients, and Ruth Seaholm, Dolores Montgomery, and Gwendolyn Reed for their excellent technical assistance.

References

1. Ham, T. H., editor: A Syllabus of Laboratory Examinations in Clinical Diagnosis: Critical Evaluation of Laboratory Procedures in the Study of the Patient, Cambridge, Mass., 1950, Harvard University Press.
2. Pritchard, J. A., and Hunt, C. F.: Surg. Gynec. & Obst. (In press.)
3. Scott, J. M.: Brit. M. J. 2: 635, 1956.
4. Finch, S., Haskins, D. M., and Finch, C. A.: J. Clin. Invest. 29: 1078, 1950.
5. Haskins, D., Stevens, A. R., Jr., Finch, S. C., and Finch, C. A.: J. Clin. Invest. 31: 543, 1952.
6. Stevens, A. R.: Personal communication to Grimes and Hutt.[7]
7. Grimes, A. J., and Hutt, M. S. R.: Brit. M. J. 2: 1074, 1957.
8. Golberg, L.: Iron in Clinical Medicine, Berkeley, Calif., 1958, University of California Press.
9. Cope, E., Gillhespy, R. O., and Richardson, R. W.: Brit. M. J. 2: 638, 1956.
10. Eastman, N. J.: Obst. & Gynec. Surv. 12: 466, 1957.

ACUTE HEMOLYTIC ANEMIA WITH CRISIS IN LABOR

Report of a Case With Review of the Literature

DENIS CAVANAGH, M.D., MIAMI, FLA.

(From the Department of Obstetrics-Gynecology, University of Miami School of Medicine, Jackson Memorial Hospital)

ACUTE hemolytic anemia is a very serious but apparently rare complication of pregnancy. In 1919 Sir William Osler[21] included a case in his survey of the severe anemias of pregnancy and the puerperium. Larrabee[16] in 1925 described a case of what was apparently acquired hemolytic anemia in pregnancy successfully treated by blood transfusion and later splenectomy. Lescher[17] in 1942 reported 8 cases of hemolytic anemia associated with pregnancy, all of which responded well to transfusion. The hematologic data associated with these cases were somewhat scant but it was felt that they represented Lederer's anemia. Most hematologists no longer regard this as a clinical entity. McCabe,[18] however, in 1956, reported a case of "Lederer's anemia," not only suggesting it to be a separate entity but also that the Coxsackie or Newcastle virus should be checked by neutralization tests as a possible etiological agent. Autoagglutinins were not found in his patient, erythrocyte fragility was minimal, and no splenomegaly was detected. The features described were those of a toxic process, with signs of hepatorenal syndrome on admission, giving a leukemoid reaction and then proceeding to aregenesis with sudden release of reticulocytes and steady improvement. Hydrocortone appeared to help recovery since no transfusions were given. Bromberg and associates[5] reported the case of a woman who had acquired hemolytic anemia in two successive pregnancies. Barnes and Doan[3] reported a case of their own, and mentioned another of Trenis and co-workers in which hemolytic anemia was treated by splenectomy during pregnancy. Alt, discussing a paper by Wolff and Limarzi,[23] mentioned a patient with congenital hemolytic anemia in whom a splenectomy was performed during the second trimester of pregnancy. The pregnancy continued to term and delivery was normal.

McElin and his collaborators[19] in a review of the literature found only 50 cases of splenectomy in pregnancy and, of these, none was for acquired hemolytic anemia and only 2 for the congenital variety. They added 3 cases of their own in which splenectomy had been performed during pregnancy for congenital hemolytic anemia. Shellhouse, Morris and Cotterman[22] reported a case in which the patient had 2 pregnancies in which hemolytic crises were treated by repeated blood transfusion. Splenectomy was performed after the

delivery of her second child and her next pregnancy was uneventful. Each of this patient's 3 children ultimately required splenectomy for hemolytic anemia, thereby emphasizing transmission of the factor as a Mendelian dominant.

Johnson and McAllister[15] described a case of congenital hemolytic anemia in crisis in the third trimester treated with multiple transfusions and resulting in the delivery of a full-term live child. O'Grady[20] reported 2 cases of hemolytic anemia, one of which was apparently congenital. This patient was treated conservatively with blood transfusions, digitoxin, folic acid, and vitamin B_{12} until after delivery of a full-term live child. Three weeks later splenectomy was performed. Their other patient, classified as having idiopathic hemolytic anemia, was delivered of a live child at term following splenectomy in the second trimester. Zachariae[24] reported the development of "subchronic hemolytic anemia" in one of his patients in 2 successive pregnancies. Frumin and associates[13] reported a case of acquired hemolytic anemia treated successfully during pregnancy with cortisone and ACTH.

Davidson[9] described a case in which megaloblastic anemia of pregnancy was superimposed on a pre-existing congenital hemolytic anemia. Drury and Geoghegan[10] reported a case in which congenital hemolytic anemia was twice complicated by megaloblastic anemia of pregnancy. Following splenectomy the patient had a normal pregnancy.

Burt and Prichard[6] reported a case of idiopathic acquired hemolytic anemia in pregnancy. After unsuccessful therapy with cortisone and ACTH, splenectomy was performed with an excellent result.

Despite this fairly extensive review of the literature, no case could be found in which an acute hemolytic episode was exhibited during labor. The following case had not been published to date because, since an autopsy on the baby had not been carried out, it was felt to be incomplete. Because of the rarity of the condition I now feel that the case merits publication.

A 36-year-old white woman (para iv, gravida vi), Group A, Rh negative, with a negative serologic test for syphilis, was admitted to Southern General Hospital, Glasgow, Scotland, on Sept. 19, 1953, at 8:00 P.M. She had planned to have her baby at home. The membranes had ruptured at 3:00 A.M. on the day of admission and she had been in desultory labor for about 18 hours when her family physician was called. The doctor had noted a fetal heart rate of about 100 per minute with associated meconium staining of the liquor amnii. Since he could find no reason for the fetal distress, he sent the patient immediately to the hospital.

The patient was in the fortieth week of this, her sixth, pregnancy, the estimated date of confinement being Sept. 25, 1953. She had been seen regularly during the prenatal period by her family physician. She had had slight vaginal bleeding from the seventh to the twelfth week of pregnancy but this had not recurred. In the thirty-fourth week she had had some ankle edema with occasional headaches but no visual disturbances. No other edema had been noted and she exhibited no hypertension or albuminuria. No other abnormality had been present except that the patient volunteered that she had been more "sunburned" than usual during August and September. No history of taking any particular drugs during pregnancy was obtained. Her previous pregnancies in 1938, 1939, and 1942 had been normal. In 1945 she had a severe attack of gastroenteritis during her fourth pregnancy and maintained that this was her only serious illness. All her children had been born at home after labors of from 4 to 12 hours and their weights were estimated at 5,455 grams, 4,091 grams, 3,523 grams, and 3,523 grams, respectively. All the babies were

apparently normal and none had been jaundiced or anemic at birth. Apart from meconium staining during her first labor which terminated in a stillbirth, all labors had been normal although apparently painless. In 1948 her fifth pregnancy terminated in abortion at the twenty-second week. No Rh antibodies had been reported during the present pregnancy. The patient's father had died of "heart disease" and her mother was alive but had diabetes. Her two brothers were well. Neither the patient nor any member of her family had had jaundice or anemia or gall bladder disease. The patient was Scottish and of Scottish ancestry.

Physical examination on admission showed that the patient's skin had a mild yellowish tinge and small telangiectatic areas were noted over the face. No edema was present and tongue and nails were normal. Her temperature was 98.8° F., pulse 104 per minute and of good quality, and respirations 22 per minute. Her blood pressure was 126/80 mm. Hg. Abdominal palpation showed the liver to extend about 4 cm. below the right costal margin although this was difficult to determine because of the proximity of the uterus. The spleen could not be felt.

The uterus was the size of about a 40 weeks' gestation, nontender and of normal tone. The fetus was engaged in the right occipitotransverse position. The fetal heart tones were heard in the right lower quadrant, the rate being 120 per minute and the rhythm regular.

On admission the patient was having no contractions and made no complaints. In view of the meconium-stained liquor which was draining from the vagina, a vaginal examination was performed. The presence of a vertex in the right occipitotransverse position at station 0 was confirmed and it was noted that the cervix was 3 cm. dilated and 60 per cent effaced. No cord prolapse was detected and no reason for the apparent fetal distress was found. The pelvis was adequate. Examination of other systems was essentially negative except for a cardiac Grade I apical systolic murmur. The urine was checked on admission and no albumin or acetone was found.

At 8:15 P.M. the patient's pulse was noted to be 120 per minute. No contractions were palpable and the fetal heartbeat was 134 per minute and regular. In view of apparent hypotonic inertia the patient was given morphine sulfate, ¼ grain hypodermically. At 8:30 P.M. blood was drawn for hematologic study with the following results: hemoglobin 4.9 Gm. per cent; erythrocyte count 2.77 million per cubic millimeter; leukocyte count 35,200 per cubic millimeter with neutrophils 93 per cent (many young forms); lymphocytes 3 per cent; myelocytes 4 per cent; the red corpuscles showed anisocytosis and polychromasia. Some cells resembled spherocytes and occasional normoblasts were seen. Platelets were noted in the smear.

No Group A negative blood could be obtained, but 1,000 c.c. of matched Group O Rh-negative blood was available for transfusion. At 9:30 P.M. the maternal pulse was 128 per minute, temperature 100.6° F., and the respiratory rate about 26 per minute. The patient about this time began to complain of feeling weak and cold and had a shivering attack. In view of rigors, tachycardia, and pyrexia in association with ruptured membranes the patient was given crystalline penicillin 300,000 units every 4 hours. Around this time the hematology report became available. The urine contained no microscopic abnormalities. It contained urobilinogen in excess but no bile. The diagnosis of acute hemolytic crisis was made before blood transfusions were started. The fetal heartbeat was being checked every 5 minutes and was last heard at 9:55 P.M. when it was 124 per minute and of good quality. At 10:00 P.M. no fetal heart tones could be heard and thick meconium-stained amniotic fluid was noted draining from the vagina. Vaginal examination revealed no cord prolapse or other mechanical cause of the apparent fetal death. By 1:30 A.M. the patient had received 1,000 c.c. of blood and she was resting comfortably although her pulse rate was 128 per minute, blood pressure 110/75, and temperature 100.4° F. Regular uterine contractions returned at 2:30 A.M. about which time the temperature was 101° F., with pulse rate 120 per minute, and respirations 24 per minute. Progressive dilatation and effacement of the cervix occurred, the second stage of labor terminating at 4:35 A.M. with the spontaneous vertex delivery of a 6 pound, 14½ ounce stillborn male child. The

placenta and membranes were delivered spontaneously at 4:55 A.M. with about 500 c.c. blood loss. The placenta and membranes were intact and normal. Careful examination of the baby showed no external abnormality but autopsy was refused.

About 12 hours after delivery, the patient's temperature was 99.2° F., with pulse 90 per minute and respiratory rate 18 per minute. She felt well although a moderately deep brownish-yellow tinge was present over the skin with minimal scleral icterus. The liver was palpable about 4 cm. below the right costal margin and not apparently tender. The spleen was just palpable. No lymph gland enlargement was detected. Despite full bacteriologic examination no pathogenic organisms were isolated from throat, vagina, cervix, or urinary tract. The urine now showed occasional erythrocytes and leukocytes. Her urinary output was normal and remained so during the entire period of hospitalization. On Sept. 21, 1953, the patient still showed typical ruddy jaundice with pallor of the mucosae. She felt very well but had noted that her stools were rather darker than normal.

Hematologic examination revealed: hemoglobin 5.2 Gm. per cent; hematocrit 21 per cent; mean corpuscular hemoglobin concentration 24.8 per cent; erythrocyte count 3.0 million per cubic millimeter; mean corpuscular hemoglobin 17.3 $\mu\mu g$; mean corpuscular volume 70 cu. μ; leukocyte count 24,900 per cubic millimeter; reticulocytes 7 per cent; direct Coombs test negative. No sickling was reported.

Leishman-stained film showed a marked polymorphonuclear leukocytosis in which many band forms and occasional myelocytes were seen. No "blast" cells were present. Many of the erythrocyte series showed polychromasia and occasional spherocytes and normoblasts were seen.

Liver function studies showed total proteins of 6.4 Gm. per cent; albumin 3.92 Gm. per cent; globulin 2.48 Gm. per cent; thymol turbidity 2 units; alkaline phosphatase 11.8 units (King-Armstrong); van den Bergh test a positive delayed direct reaction; bilirubin 1.0 mg. per cent; cephalin cholesterol flocculation test negative. The Wassermann and Kahn tests were negative.

Blood grouping was checked by the National Blood Transfusion Service and found to be Group A, Rh negative. Residual blood in bottles used for transfusion on the night of admission was rematched and compatibility confirmed with no bacterial growth reported. A further 500 c.c. of compatible blood was given slowly.

On Sept. 24, 1953, the patient was comfortable. The jaundice was less marked although the mucosae were still pale. The liver was now just palpable below the right costal margin but the spleen was significantly enlarged.

Hematologic examination revealed: hemoglobin 6.4 Gm. per cent; hematocrit 24 per cent; mean corpuscular hemoglobin concentration 26.7 per cent; leukocyte count 18,000 per cubic millimeter; reticulocytes 6 per cent. Examination of the urine showed urobilinogen in excess but no other abnormality. Penicillin therapy was discontinued. A further 500 c.c. of matched blood was given. Iron and ammonium citrate, 20 grains three times a day after meals, and ascorbic acid, 50 mg. three times a day, were prescribed.

On Sept. 29, 1953, the skin icterus had almost cleared, the hemoglobin was 7.7 Gm. per cent; erythrocyte count 3.03 million per cubic millimeter; leukocyte count 11,800 per cubic millimeter; examination of the urine was negative. The liver was just palpable but considerable splenomegaly persisted.

Sternal marrow examination was done on September 29 and revealed extreme cellularity with marked normoblastic hyperplasia. All varieties of normoblasts were seen with the early forms more frequent than normal. Some cells were large and showed early hemoglobinization. Leukopoiesis was active but no abnormal maturation was apparent. The bone marrow was considered to be consistent with acute hemolytic anemia.

On September 29 the red-cell fragility was estimated. Hemolysis commenced at a concentration of 0.56 per cent NaCl and was complete at 0.44 per cent NaCl. (The normal range was 0.42 to 0.32 per cent NaCl.) The erythrocyte sedimentation rate was 35 mm. at end of the first hour and 53 mm. at the end of the second hour. Fecal urobilinogen was increased to 348 mg. in 24 hours.

On Oct. 6, 1953, the tip of the spleen was still palpable but otherwise clinical examination was negative. The hemoglobin was 9.6 Gm. per cent; leukocyte count 9,400 per cubic millimeter. The red-cell fragility test showed hemolysis starting at 0.52 per cent NaCl and complete at 0.36 per cent NaCl the control range being 0.47 to 0.3 per cent NaCl.

On October 7, the eighteenth postpartum day, the patient was allowed home on iron and vitamin C therapy.

On October 29, the patient returned to the hematology clinic. She felt well and physical examination showed no abnormality. The hemoglobin was 12.9 Gm. per cent; erythrocyte count 4.63 million per cubic millimeter; leukocyte count 9,200 per cubic millimeter. At her routine postpartum visit no abnormalities were found.

On Jan. 21, 1954, the patient was again seen at the hematology clinic. Her menses had returned, the first being normal and the second being fairly heavy with a few clots passed but lasting the usual 4 days. The hemoglobin was 12.8 Gm. per cent; erythrocyte count 4.59 million per cubic millimeter; leukocyte count 9,400 per cubic millimeter. Physical examination revealed no abnormality.

Comment

An excellent general discussion of acute hemolytic anemia with particular reference to its occurrence during pregnancy has recently been given by Burt and Prichard.[6] Generally, the antihuman globulin test (direct Coombs) is positive in acquired hemolytic anemia while it is usually negative in congenital spherocytosis.[8]

Despite the negative direct Coombs test and in the absence of a family history of spherocytosis, the case reported here is regarded as one of idiopathic acquired hemolytic anemia with a crisis developing during labor. It seems most likely that fetal death in utero resulted from acute hypoxia. Hemolytic anemia is not a very rare condition as is illustrated by the fact that Gänsslen and associates[14] were able to study about 120 cases of the familial variety in southern Germany. In 1944 Elliot[12] reported that minor increases in osmotic fragility may be found in normal pregnant women. In view of these facts, it seems amazing that more instances of acute hemolytic anemia in pregnancy have not been reported and suggests that pregnancy in some way confers protection against certain hemolytic mechanisms.

With regard to the precipitation of the acute hemolytic process in this case, it seems unlikely that the morphine sulfate can be incriminated as it might be in a sickle-cell crisis for the mechanism of hemolysis is different in this latter condition.[1]

Castle and co-workers[7] showed that injurious substances of ischemic tissue origin may cause hemolysis by increasing the osmotic and mechanical fragilities of erythrocytes. Thus, in this patient, it seems possible that the ischemia present during uterine contractions may have initiated the hemolytic process. Another interesting, although unlikely, possibility is maternal infection, in association with ruptured membranes, causing hemolysis. Betke and collaborators[4] described a case of acute hemolytic anemia in which a Coxsackie virus was isolated from the feces and neutralization antibodies demonstrated in the serum during convalescence. The case reported by McCabe[18] is also interesting in this respect. While the bulk of the evidence in this case seems to favor the diagnosis of idiopathic acquired hemolytic anemia, it seems unfortunate in retrospect that this patient was not checked for spherocytosis and reticulocytosis when last seen 6 months after delivery. If these features had been found in the presence of a normal count, this would have provided strong confirmatory evidence of congenital hemolytic anemia.

If these had been found together with even minimal splenomegaly then splenectomy would be the treatment of choice.

In the management of a patient with hemolytic anemia associated with pregnancy, the following plan of therapy may be followed: It must be emphasized that the differential diagnosis between the congenital and acquired types is very important. Splenectomy is the treatment of choice in the former but is generally not indicated in the latter. In acquired hemolytic anemia the most important point in therapy is withdrawal of the noxious agent, if identified, although some respond to ACTH and cortisone. Where the patient does not respond or becomes refractory to steroid therapy, splenectomy may be of value. When the diagnosis of congenital hemolytic anemia is made in the first or second trimester, splenectomy is the treatment of choice. If the condition is found in the third trimester, conservative therapy until delivery and then postpartum splenectomy probably constitute the treatment of choice.

Conclusions

Any form of acute anemia in the mother results in acute hypoxia for the fetus in utero. In the present case, this was reflected in the slow fetal heart rate reported prior to admission and in the meconium staining of the liquor amnii. At any time during a hemolytic crisis the fetus may succumb to the hypoxia whether in pregnancy or in labor. Thus, any patient in crisis who has a viable fetus should be watched carefully for the development of signs of fetal distress and the pregnancy terminated by forceps or cesarean section, depending upon the stage of labor reached and the condition of the mother.

The main problem presented in acute hemolytic anemia in pregnancy is that of replacing hemoglobin to a blood volume greater than would be found in the nonpregnant state. For these reasons the patient has to be treated vigorously to accomplish diuresis while hemoglobin is being replaced slowly with packed cells. The object of the treatment is to raise the hemoglobin level to a point safe for delivery without overloading the cardiovascular system or precipitating further hemolysis. The over-all plan of therapy in these cases is (1) blood replacement; (2) antibiotics to prevent infection; (3) vigorous treatment of such complicating factors as pre-eclampsia; (4) continuous oxygen therapy for the fetus during a crisis; (5) consideration of cesarean section under regional anesthesia for the fetal distress during the hemolytic episode, if the mother's condition permits and the child is viable; (6) postpartum care should be directed toward gradual blood replacement and general therapy. The patient's condition should be reassessed after about 6 months in regard to hematologic status and the presence of splenomegaly. In the presence of congenital hemolytic spherocytosis or even idiopathic hemolytic anemia resistant to steroid and other therapy, splenectomy is the treatment of choice. Since neither acquired nor congenital hemolytic anemia is adversely affected by pregnancy, there is no indication for therapeutic abortion or sterilization.

In closing, it should be emphasized that any pregnant patient with an acute hemolytic process should be checked for sickle-cell anemia, for with this condition there is a fetal mortality of 40 per cent and one pregnancy in 10 ends in maternal death.[11] Thus, it is suggested that any pregnant Negro woman with anemia, or even bizarre symptoms should have a sickle-cell blood

smear made to check for "sickling." If this is positive, then the patient has either the trait or the disease. Even if the preparation shows no "sickling," paper electrophoresis should be carried out to ensure that hemoglobin S-C disease is not being missed. Rarely thalassemia minor gives trouble but here the diagnosis can be established by chemical methods and morphology. It is interesting that in this sickle-cell group of diseases, the erythrocytes exhibit decreased fragility in hypotonic saline solutions. In patients with sickle-cell disease, weekly hematologic examinations are essential with iron therapy as required and blood transfusion only if the hemoglobin falls below 8 Gm. per cent or crisis develops. ACTH and cortisone should not be used for they may actually precipitate crises. All infections should be treated vigorously. Oxygen should be given during crises and digitalization is advisable in impending heart failure. Even slight anoxemia may precipitate a sickle-cell crisis and so during labor oxygen should be given liberally, sedation reduced to a minimum, and the patient delivered under pudendal nerve block anesthesia. It should be mentioned that toxemia of pregnancy is more common in these patients and the combination of eclampsia and hemoglobinopathy is obviously a very dangerous one.[2] Postpartum hemorrhage is not unlikely and the use of oxytocics or more particularly of peripheral vasoconstrictors such as norepinephrine may precipitate a sickle-cell crisis. While therapeutic abortion is generally considered unjustifiable, the undesirability of further pregnancies in these patients seems obvious. Fortunately, sickle-cell anemia is rarely found in association with pregnancy and up to 1956 only about 138 cases had been reported.[11] The reason for the relative infertility in these women may be explained by the fact that many of them die young or become such chronic invalids that the possibilities of marriage and impregnation are much reduced. A careful analysis of cases reported in which maternal deaths have occurred suggests that a great many of these women had hemoglobin S-C disease rather than true sickle-cell anemia or sickle-cell trait. In the future this question will be answered through utilization of hemoglobin electrophoretic studies.

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References

1. Adams, J. Q., Whitacre, F. E., and Diggs, L. W.: Obst. & Gynec. 2: 335, 1953.
2. Adams, J. Q.: South. M. J. 50: 898, 1957.
3. Barnes, A. C., and Doan, C. A.: Am. J. Obst. & Gynec. 55: 864, 1948.
4. Betke, K., Richarz, H., Schubothe, H., and Vivell, O.: Klin. Wchnschr. 31: 373, 1953.
5. Bromberg, Y. M., Toaff, R., and Ehrenfeld, E. N.: J. Obst. & Gynaec. Brit. Emp. 55: 325, 1948.
6. Burt, R. L., and Prichard, R. W.: Obst. & Gynec. 10: 444, 1957.
7. Castle, W. B., Ham, T. H., and Shen, S. C.: AECU 874, Oak Ridge, 1950, U.S. Atomic Energy Commission.
8. Davidsohn, I., and Oyamada, A.: Am. J. Clin. Path. 23: 101, 1953.
9. Davidson, L. S. P.: Edinburgh M. J. 59: 315, 1952.
10. Drury, M. I., and Geoghegan, F.: Brit. M. J. 2: 393, 1957.
11. Eisenstein, M. I., Posner, A. C., and Friedman, S.: Am. J. Obst. & Gynec. 72: 622, 1956.
12. Elliot, G. A.: J. Obst. & Gynaec. Brit. Emp. 51: 198, 1944.
13. Frumin, A. M., Smith, E. M., Taylor, A. G., and Dratman, M. B.: Am. J. Obst. & Gynec. 65: 421, 1953.

14. Gänsslen, M., Zipperlen, E., and Schüz, E.: Deutsches Arch. klin. Med. **146**: 1, 1925.
15. Johnson, H. H. C., and McAllister, J. E.: Canad. M. A. J. **65**: 377, 1951.
16. Larrabee, R. C.: Am. J. M. Sc. **170**: 371, 1925.
17. Lescher, F. G.: Lancet **2**: 148, 1942.
18. McCabe, E. S.: Am. Pract. & Digest. Treat. **7**: 1609, 1956.
19. McElin, T. W., Mussey, R. D., and Watkins, C. H.: AM. J. OBST. & GYNEC. **59**: 1036, 1950.
20. O'Grady, J. W., Riva, H. L., and Ritzenthaler, J. G.: AM. J. OBST. & GYNEC. **65**: 1338, 1953.
21. Osler, W.: Brit. M. J. **1**: 1, 1919.
22. Shellhouse, M., Morris, H. R., and Cotterman, V. L.: J. A. M. A. **145**: 1065, 1951.
23. Wolff, J. R., and Limarzi, L. R.: AM. J. OBST. & GYNEC. **51**: 447, 1946.
24. Zachariae, F.: Acta obst. et gynec. scandinav. **32**: 250, 1953.

FETAL DISTRESS*

JAMES WALKER, B.Sc., M.D., F.R.C.O.G., DUNDEE, SCOTLAND

(From the University of St. Andrews, Scotland, and the Department of Obstetrics and Gynaecology, Queen's College, Dundee)

IN RECENT years improvement in social conditions in the civilized world and greatly improved maternity care have caused dramatic falls in the rates of maternal mortality, stillbirth, and early neonatal death.

The good clinician is concerned now with the quality of the child produced. Stillbirth is a measurable failure, but what of the various degrees of permanent anoxic damage, subtle in their effects but far reaching in their importance? This is a much less finite problem: measures are difficult and clinical standards impossible to apply.

In these days of expanding technology and rising standards of achievement, there is a desperate need that all infants go home from the hospital with the expectation of maximum mental prowess and of minimal behavioral abnormality to which they are entitled by their genetic potential.

The maximum risk of long-term damage is, in general, to the premature baby, not only because of its prematurity and the risks allied thereto, but because also of damage antenatally. Genetic defect or early pregnancy insult can lead to damage. These are vast problems in themselves—but I am concerned in this paper mainly with the problems of later pregnancy. During prolonged or difficult labor[35] and in the presence of gross disease in the mother, it is possible that metabolic damage to the baby may occur; and I fully realize the implications of birth trauma. I am in this paper, however, concerned only partly with trauma, and mainly with anoxia.

The fetus in utero under normal circumstances grows and develops normally at oxygen levels low by adult standards, but it must be clearly realized that such levels are physiological in the fetus. There are, however, many circumstances under which the oxygen supply can deteriorate, often very rapidly. Associated with, because of, or following from, these circumstances, the fetus usually shows the classical signs of distress.

The Classical Signs of Fetal Distress

Meconium.—A hundred years ago Schwartz[49] in a masterly treatise described the clinical situations under which meconium was passed. He suggested that some change in fetal physiology was responsible and stated: "The

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presence of meconium is always proof of the suppression or reduction of respiratory placental communication and is a reliable sign of death of the fetus or of an endangering of life in the act of birth."

Heart.—Following on the recognition of the fetal heart sounds by Mayor[38] and Kergeradec,[27] the fetal heart rate regularly has, over the last hundred years, been used as a monitor of fetal well-being.[7, 28, 32, 56]

Recent Research

It has become clear in recent years that we must study the physiological state of the distressed child. If we could understand the condition of the child at the time distress is manifest, we might be able to avoid unnecessary interference or by earlier interference obtain a child not only alive but mentally not impaired.

Many workers all over the world have instituted special study of the physiology of the fetus directly or indirectly related to its oxygen supply or to the damaging effects of anoxia.[4, 6, 9-14, 21, 22, 24-26, 34, 36, 39, 41-45, 51, 62, 64-66]

The Oxygen Physiology

Any discussion of fetal distress should be preceded by a consideration of the oxygen physiology concerned, and above all by an outline of the essential features of the fetal circulation.

We are greatly indebted to Barclay, Franklin, and Pritchard[2] and more especially to the brilliant recent work of Dawes, Mott, and Widdicombe[17] for the details of the fetal circulation in the lamb. In the lamb the levels of oxygen saturation in the umbilical vessels in late pregnancy are somewhat higher than those usually found in human pregnancy, i.e., the per cent saturation with oxygen of the blood in the lamb umbilical vein and artery are 80 and 58 per cent respectively,[17] but in the human at the thirty-eighth to thirty-ninth week the corresponding readings are 70 and 30 per cent,[18, 39, 43, 58, 59] or 80 and 40 per cent.[34, 47, 48]

It must be, however, obvious that the blood reaching the fetal brain and heart muscle is less saturated with oxygen than that in the umbilical vein. In the lamb Dawes measured carotid saturation directly and found that the carotid blood, that is the blood supplying the brain and heart muscle, is 62 per cent saturated with oxygen. This is the level at which the lamb lives, not at the 80 per cent of the umbilical vein, but some 20 per cent lower; similarly in the human baby the carotid and coronary blood oxygen saturation should be close to 50 per cent only.

The reason for the marked drop in oxygen per cent saturation of the blood between the umbilical vein and the carotid artery is explained by the detail of the circulation.[59]

The Carotid Artery Saturation

Dawes[16] in a fascinating series of experiments has measured the per cent saturation of the blood in the umbilical vein, carotid artery, and umbilical

artery under a wide variety of conditions of oxygen level and has shown that the carotid artery saturation remains in a fairly constant relationship to the umbilical *artery* saturation, no matter the levels in the umbilical vein. In the lamb the carotid artery saturation is usually about 5 per cent higher than that in the umbilical artery. Dawes can measure the carotid artery saturation directly in the lamb, but in the human fetus, where this is not possible, it appears to be fairly close to the truth to assume that the carotid artery saturation is 5 to 10 per cent higher than that in the umbilical artery *under all circumstances of oxygen level.*[1]

If we accept this assumption, and it is fair that we do so without proof to the contrary, we are then in a position to estimate the *carotid artery* saturation if we know the per cent saturation with oxygen of the blood in the umbilical *artery.* This relationship, as I will show later, is of immense value in appreciating some of the unusual oxygen levels seen in distressed babies.

By utilization of the published figures of dissociation curves for the fetal sheep[5] and human fetus[6] we find the likely levels of oxygen tension at which the human fetus lives and develops (Table I). Measurements of the oxygen levels in the maternal blood of the intervillous space before the onset of labor[61] suggest very strongly that the levels found at the time of birth in the fetal vessel are very close to, if not identical with, those pertaining in utero before labor or delivery begins.

It appears, therefore, that normally in late pregnancy the oxygen levels in the blood of the fetus are moderately high. They have, however, been shown to be affected usually in a downward direction by certain abnormal conditions, e.g.: (1) *rising gestational age especially in primigravidas over 25 years of age;*[34, 37, 39, 43, 54, 62] (2) *previous threatened abortion;*[55] (3) *maternal pre-eclampsia;*[34, 57, 62] (4) *labor* which, if normal, appears to have little effect,[18, 34, 58] but, if prolonged or mechanically difficult, may depress the supply; (5) *anesthesia.*[20, 53, 63]

TABLE I. PER CENT SATURATION WITH OXYGEN OF THE BLOOD IN THE MAJOR FETAL VESSELS IN LATE PREGNANCY BEFORE TERM. LAMB AFTER DAWES, MOTT, AND WIDDICOMBE[17]; HUMAN, SEE SCRIPT

	LAMB (%)	HUMAN (%)	
Umbilical vein	80	70	80
Umbilical artery	58	35	40
Carotid artery	62	45	50
	(po_2 30 mm. Hg)	(po_2 22-25 mm. Hg)	

It can be seen, therefore, that because of these proved factors many babies will be born with oxygen levels in their cord vessels very much below the expected ideal normal.[59]

The Oxygen Levels in the Cord Blood at Birth Where Delivery Follows Immediately on Clinical Fetal Distress

I divide distress, clinically, into four groups:

1. Distress Associated With Cord Strangulation and Entanglement.—This diagnosis can be made only in retrospect but occurs in my series in 2.5 per

cent of the labors of primigravidas and 1 per cent of the labors of multigravidas. Under these circumstances there is interference with umbilical flow and possibly some hemodynamic changes in the fetal circulation. The oxygen situation is as seen in Fig. 1.

A. The venous umbilical oxygen saturation remains reasonably normal as there is no interference with transplacental transfer of oxygen. The level may in fact rise if fetal heart slowing is also present.[3]

B. The arterial reading is very low, and, correspondingly, if our assessment of the circulatory pattern is correct, the carotid saturation would be very low. This pattern has been previously described at least by Haselhorst and Stromberger,[23] Clemetson and Churchman,[13] and by McKinney and associates.[37]

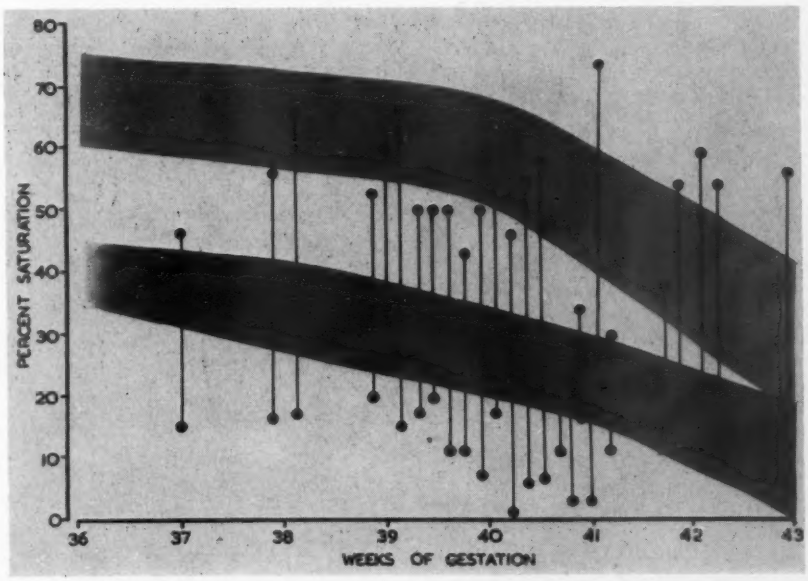

Fig. 1.—Oxygen findings in a series of cases where fetal heart slowing was proved to be due to cord strangulation or entanglement. The upper shaded area is the normal range of umbilical vein readings to be expected; the lower shaded area the normal umbilical arterial readings.

2. Slowing of the Fetal Heart Rate as a First Sign.—Slowing of the fetal heart occurs probably under these clinical situations:

A. Pressure on the advancing fetal head—bony or soft tissues, as so beautifully shown by Yagi[66] and Hohn.[26]

B. Secondary to cord strangulation as previously described (12 per cent of all cases of slowing).

C. In the presence of gross fetal anoxia for any reason—when the oxygen tension in the carotid artery blood falls sufficiently low.

Under those circumstances the oxygen pattern is very like that of the "cord" cases (Fig. 2). In most of my cases clinical situation A was present and the umbilical venous reading remained high, indicating normal transplacental oxygen transfer, but the umbilical arterial oxygen was very low, indicating gross interference with fetal oxygenation. The mechanism by which this poor oxygen level appears in the artery is not fully understood. The carotid saturation under these circumstances is likely to be very low. Dawes and his colleagues propose to investigate this situation experimentally in the coming spring.

TABLE II. FETAL MORTALITY IN RELATION TO FETAL DISTRESS IN PRIMIGRAVIDAS

TYPE OF DISTRESS	WEEK OF GESTATION: UP TO AND INCLUDING 38TH — NO. OF CASES	UP TO AND INCLUDING 38TH — SB/NND*	39TH AND 40TH — NO. OF CASES	39TH AND 40TH — SB/NND	41ST AND LATER — NO. OF CASES	41ST AND LATER — SB/NND	UNCERTAIN — NO. OF CASES	UNCERTAIN — SB/NND	TOTAL — NO. OF CASES	TOTAL — SB/NND	%	CESAREAN SECTION	FORCEPS
Meconium alone	12	6 (2 IUD†)	47	6 (2 IUD)	181	9 (4 IUD)	32	3	273 (less 8 IUD)	24	8.8	15	38
										16	5.9		
Slowing heart alone	28	3	64	0	157	2	21	0	270	5	1.9	5	96
Rapid heart alone	3	0	12	0	32	1	7	2	54	3	5.5	5	19
Meconium plus slow heart	13	2	30	1	121	9	27	2	191	14	7.3	11	54
Meconium plus rapid heart	1	0	11	3	23	4	3	0	38	7	18.4	3	14
Meconium first	20	6 (2 IUD)	72	9 (2 IUD)	262	15 (4 IUD)	46	5	400	35 (less 8 IUD)	8.8		
											6.8		
Slow heart first	32	5	86	0	208	8	37	0	363	13	3.6		

*SB/NND, stillbirth and neonatal death.

†IUD means that there was intrauterine death of the fetus before the onset of labor.

In some of our cases clinical situation C was present and both levels were very low indeed (Fig. 2).

I would like to point out that, in our cases, if the passage of meconium by the fetus has clearly *followed immediately* on a period of fetal heart slowing the oxygen pattern is unchanged and is that of the slow fetal heart group. This is a different pattern from that seen when meconium staining is the first sign, as I will show later.

3. Rapidity of the Fetal Heart Rate as a First Sign.—This occurs in two clinical situations:

A. As an early sign of anoxia—often in long labors—preceding the passage of meconium.

B. Associated with maternal pyrexia and tachycardia: (1) With intrauterine infection, and then the fetal tachycardia indicates fetal infection as so beautifully shown by Smith and co-workers.[50] (2) With extrauterine infection, as is seen clinically in the presence of serious material infection, e.g., infective hepatitis or pyelonephritis, possibly indicating a toxic effect on the fetus. I have no oxygen studies in these cases but as I will show later this type of case, if associated with meconium, is clinically very worrying.

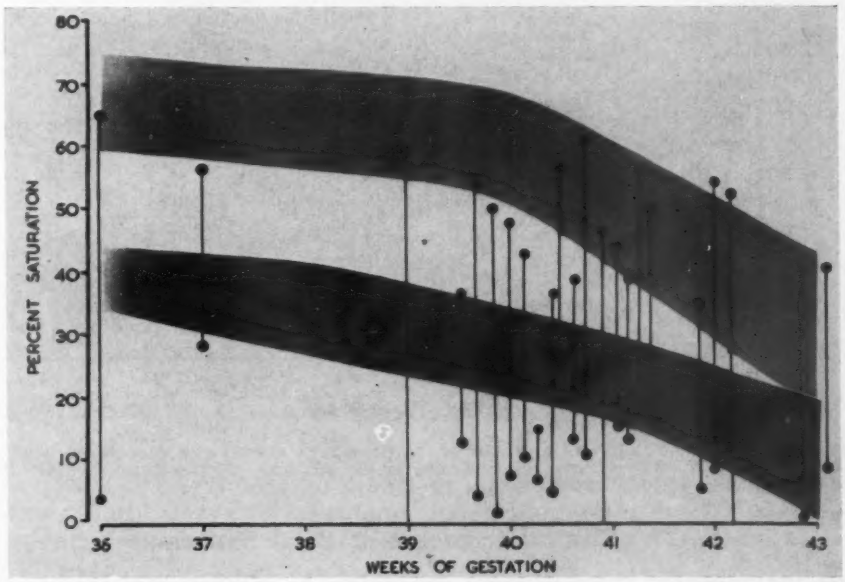

Fig. 2.—Oxygen findings in a series of cases where fetal heart slowing below 100 beats per minute, with or without irregularity, was the only sign of distress, and there was no evidence of cord entanglement or strangulation.

4. Meconium as a First Sign.—My experience and studies strongly suggest that this is a sign of interference with the transplacental transfer of oxygen. The mechanism of this sign is not understood. Windle[65] states that the newborn monkey intact within its gestation sac will pass meconium during a period of oxygen deprivation. In the lamb[16] and in the adult human active bowel movement is seen only in the terminal stages of anoxia from which recovery is rare. This cannot be true of the human fetus as the fetal mortality is low in cases where the passage of meconium is the only sign of distress (Table II). I think it is fair to say that at this stage in our knowledge we have little certain information as to the mechanism whereby a fetus can empty the whole of its large bowel steadily into the amniotic sac. It appears

from my studies to be associated with a deficiency of oxygen mainly differentiated from other types by a very low reading in the blood of both vessels (except as noted following slowing of the fetal heart). The oxygen pattern (Fig. 3) is identical with that seen in the lamb when the oxygen in the mother's inspired air is much reduced,[1] i.e., (a) the umbilical *vein* oxygen is low; (b) the umbilical artery oxygen is very low; and (c) the carotid saturation must be very low indeed. If fetal heart slowing *follows* the passage of meconium the oxygen levels and pattern remain the same.

I would like to point out that these oxygen levels in meconium-staining cases are not confirmed by other workers. In some cases[39] the arterial levels were not shown. McKinney,[37] however, reports both vein and artery readings and does not find any depression of oxygen saturation.

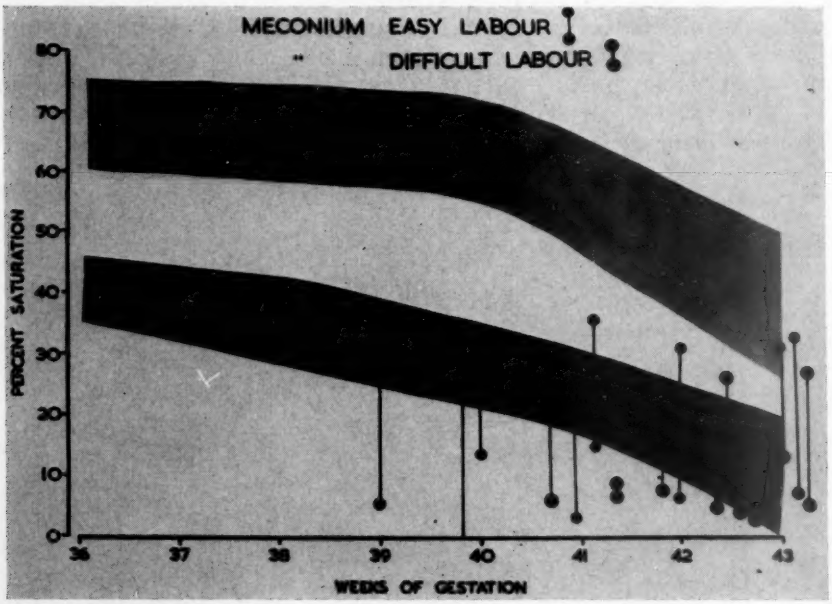

Fig. 3.—Oxygen findings in a series of cases where there was meconium staining only as a sign of distress. There was no irregularity or slowing of the fetal heart. This is a mixed group of easy and difficult labors.

The Clinical Incidence of Fetal Distress

The incidence of fetal distress varies, as do most obstetrical phenomena under the standard situations of gestational age, parity, maternal age, and type of labor. There are, however, other interesting clinical associations.

By Gestational Age, by Type of Labor in Primigravidas.—In 1954 I showed that the over-all incidence of fetal distress (of all types) rises steadily as gestation becomes prolonged. At 40 weeks' gestation only 8.4 per cent of cases showed distress but by the forty-fourth week distress was manifest in 25.9 per cent of all labors.

In difficult labor by the forty-third week nearly 40 per cent of the babies showed distress as against 20 per cent where labor was easy and spontaneous. The increased incidence in prolonged labor is shown also by Lister and Buchanan.[29]

By Gestational Age and Maternal Age, by First Signs of Distress.—In primigravid labors there is a steady rise in the incidence of distress with slowing of the heart or meconium as a first sign, both when plotted against rising

gestational age and against rising maternal age (Fig. 4). These rises are independent of each other. For example, the incidence of meconium staining as a first sign rose from 2 per cent in 101 primigravidas under 20 years of age in labors up to the thirty-eighth week, to 44 per cent in 25 primigravidas over 35 years of age delivered in the forty-second and later weeks.

With the Spontaneous Onset of Labor.—In view of the high incidence of induction in my series, the spontaneous onset group excludes most clinically abnormal pregnancies but also excludes any influence of induction. The general pattern is, however, exactly similar. For example, the incidence of meconium staining of the liquor in the labors of primigravidas under 20 up to the thirty-eighth week is 1 per cent (in 93 cases) rising to 41 per cent (7 in 17 cases) in primigravidas over 35 delivered in the forty-second and later weeks. The total incidence is 8.4 per cent when meconium is the first sign, and change in the heart rate 8.2 per cent.

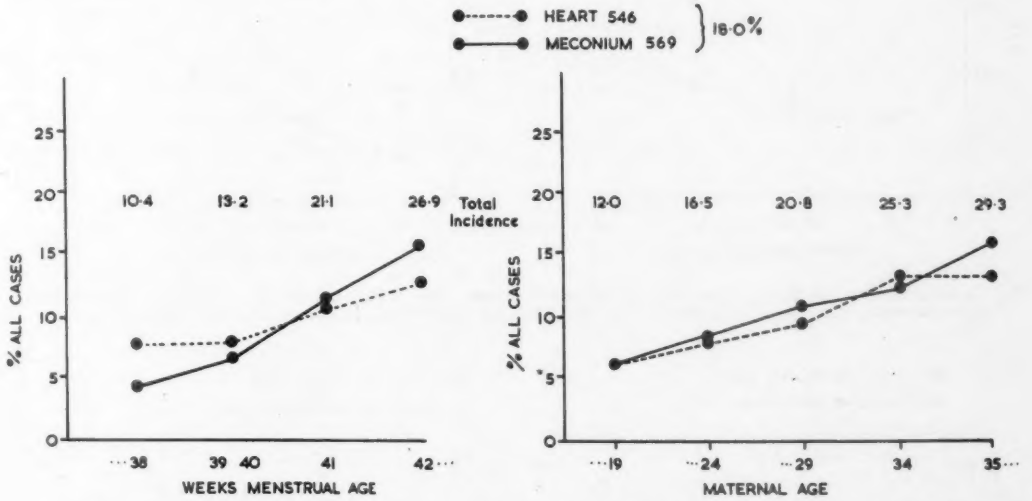

Fig. 4.—Incidence of fetal distress in the labors of 6,189 primigravidas. Cases are distinguished as to whether fetal heart slowing or meconium appeared as the first sign of distress.

With Induced Labor.—Where labor is induced by artificial rupture of the membranes (hindwaters) the incidence of fetal distress is 27.7 per cent. In 14.1 per cent meconium is the first sign and in 13.6 per cent the heart rate (usually slowing) (Fig. 5).

Meconium.—In more than half the cases in which the passage of meconium is the first sign of distress, meconium was already present in the liquor at the time of rupture of the membranes so that, whatever the reason for the meconium, it was not due to the fact of the induction. It is seen from Fig. 5 that the frequency with which meconium is found is very close to the overall incidence of meconium staining in labors proceeding to spontaneous onset, and in fact up to the end of the thirty-eighth week the incidence is higher.

In Fig. 6 is seen the incidence of both signs of distress in cases of induced labor, depending on the state of the cervix at the time of induction.

There is little difference in the incidence of meconium staining. With both types of cervix about half the cases at each stage of pregnancy show meconium at the time of rupture of the membranes. The incidence of meconium staining in induced labors appears unrelated to the state of the cervix.

The Heart.—It is seen in Fig. 5 that there is a greater incidence of slowing of the heart in labors induced by artificial rupture of the hindwaters. It is a little difficult to feel certain that the high rate up to the thirty-eighth week is completely representative as it is obtained in 9 out of a total of 73 cases. There is clearly, however, in the forty-first and forty-second weeks a definitely greater incidence of distress of this type.

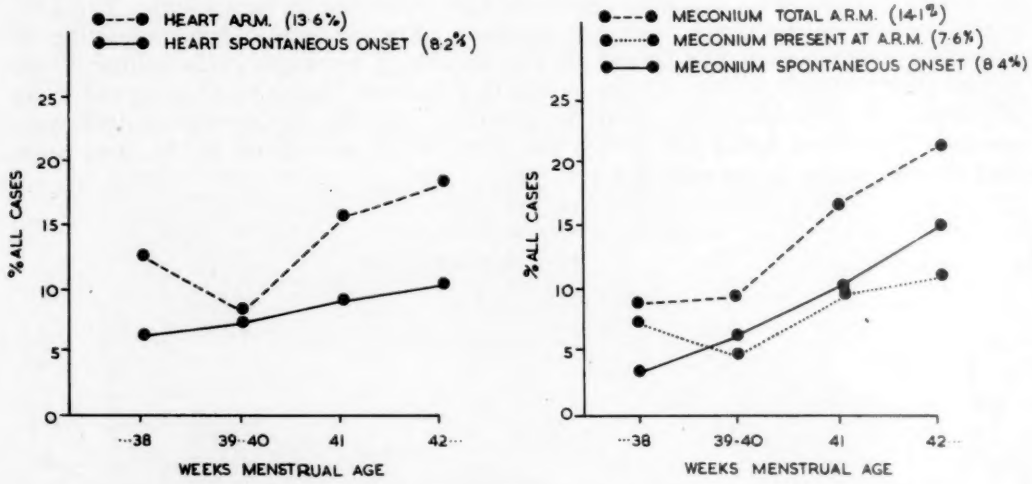

Fig. 5.—Incidence of fetal distress in primigravidas. In 5,328 cases the onset of labor was spontaneous and in 750 labor was induced by artificial rupture of the hindwaters.

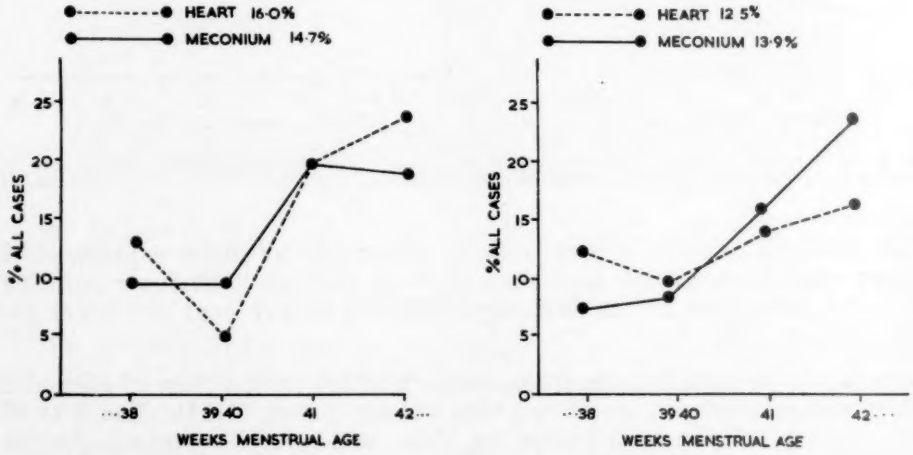

Fig. 6.—Incidence of fetal distress in induced labor in primigravidas depending on the state of the cervix at the time of induction. The graph on the left represents 231 with unripe cervices, that on the left 519 with ripe cervices.

Fig. 6 suggests that although the incidence following induction in cases in which the cervix is ripe is a little higher than the over-all incidence after the spontaneous onset of labor (Figs. 5 and 6), the main reason for the high incidence in cases of induced labor in the forty-first and later weeks is the increased risk of distress in induced labor with an unripe cervix at the time of induction.

Comment

What, therefore, is the meaning of all these findings? If we accept for the moment that:

A. Meconium staining, as a first sign of distress, is due to deficiency of oxygen transfer across the placenta, we can say:

1. Oxygen transfer in labor deteriorates in late pregnancy and deteriorates more with advancing maternal age.

2. In induced labor oxygen transfer appears to be less efficient than in cases allowed to proceed to the spontaneous onset of labor. Most patients in whom labor is induced have some clinical abnormality—pre-eclampsia, hypertension, bleeding in labor, etc., or are over 25 years of age, conditions well known to interfere with fetal oxygen levels.[34, 57, 62] This could explain the high incidence of meconium staining before the onset of labor and the greater incidence of meconium staining in induced labor.

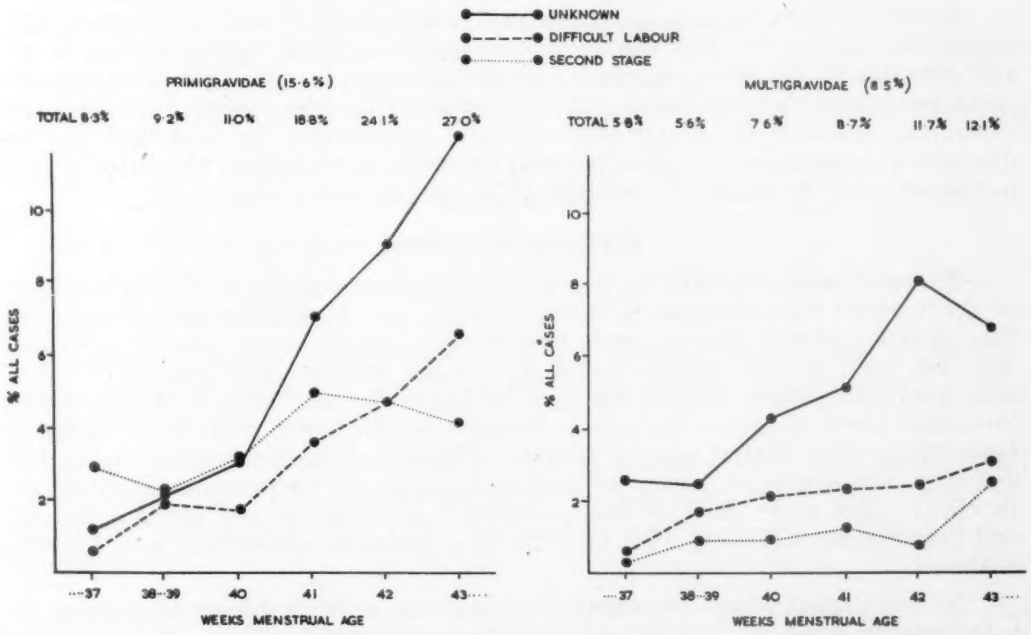

Fig. 7.—Incidence of fetal distress in the labor of 5,254 primigravidas and 5,312 multigravidas. The clinical cause of the distress has been assessed in each individual case.

B. That fetal heart slowing is due to difficulty in labor and mainly to pressure on the fetal head by bony and soft pelvic tissues, then we can say that:

1. This parallels the known increase in difficult labor which is seen with advancing gestational age.

2. Induction of labor somehow or other increases the likelihood of difficult labor with fetal head pressure. This is in fact seen when we study the incidence of cesarean section in difficult induced labor, especially where the cervix is unripe at the time of induction.[60]

Incidence of Fetal Distress by Clinical Cause.—These theoretical deductions receive some further consideration when we study the incidence of distress with rising gestational age in cases where the clinical cause of the distress

has been assessed by a study of each individual case (Fig. 7). I have excluded from the diagram cases associated with obvious disease, e.g., accidental hemorrhage and interference with cord circulation.

In *primigravidas* it is seen that: (a) The incidence of distress due to difficult labor is about 2 per cent up to the fortieth week and rises steadily to 6.6 per cent by the forty-third week. (b) The incidence of fetal heart slowing in the second stage of labor (a late pressure effect) rises from 3.3 per cent at 40 weeks to 5.1 per cent at 41 weeks and then falls slightly. (c) The incidence of meconium staining, where there was no clinical explanation in the pregnancy or labor, rises fairly steadily from 1.1 per cent up to the thirty-eighth week to 11.2 per cent by the forty-third and later weeks.

In *multigravidas* there is practically no distress caused by difficult labor or head pressure in the second stage (although both are seen where the previous pregnancies have been only abortions). The incidence of meconium staining without clinical explanation, however, rises steadily from 2.5 per cent up to 38 weeks to 8.3 per cent of deliveries in the forty-second week and then falls.

These findings in primigravidas and multigravidas help to confirm the suggestion that: (1) The rise in the incidence of fetal heart slowing is essentially due to the rising incidence of difficult labor in primigravidas as both gestatonal age and maternal age increase. (2) The rising incidence of meconium staining by gestational age and presumably by maternal age is due to a deterioration in transplacental oxygen transfer since the pattern and incidence are very similar in primigravidas and multigravidas.

Perinatal Mortality

The perinatal mortality in our series gives some guide to the importance of the various clinical signs as interpreted by us. It must be noted that over this period signs of distress were looked upon as of serious import and had this not been so the results might have been worse. The results in 5,254 primigravidas (single births) are seen in Table II. Included in the table are the cases where cesarean section or forceps delivery was performed *within 2 hours of the first clinical sign of distress.* This shows the cases where operative delivery was indicated solely or mainly because of the presence of distress. In many other cases distress was manifest late in the second stage of labor, and spontaneous delivery, with or without a generous episiotomy, was rapidly achieved.

In some cases where meconium staining was present during the course of a prolonged labor its importance was not appreciated. There were, for example, 32 cases where labor had lasted 24 hours (and delivery would be possible only by cesarean section) and meconium staining was known to be present. In 13, cesarean section was performed and all babies were saved. In 19, where labor was allowed to proceed (often for many hours) in an attempt to achieve a vaginal delivery, 6 babies were lost.

Table II shows many important clinical points: (1) Although less common in the premature labor, fetal distress when present is of serious import for the baby. Most of the "meconium" cases were examples of antepartum hemorrhage or pre-eclampsia. In fact, when in such cases the fetus passes meconium, the outlook is very poor indeed. The seriousness as a "sign," however, becomes less the longer pregnancy progresses. There are many possible interpretations of this finding. (2) Fetal heart slowing alone is of minimal risk to the baby, provided delivery is achieved soon. In 220, or 82 per cent, of the cases where fetal heart slowing was the only sign of distress, the labor was already in the second stage, so that delivery could be rapidly

achieved. In most of the others the slowing was not persistent over a long period. (3) Fresh meconium alone still presages fetal death in a high proportion of cases. Even in the cases where the meconium is followed by slowing or rapidity of the fetal heart and the risk increases, those fetal heart changes often precede fetal death only by a very short period, not long enough to allow delivery to be safely achieved.[29, 45, 52, 58] (4) The most significant risks occurred in the cases where meconium was associated with a rapid fetal heart rate. The severe cases are mixed; at least one was associated with cord entanglement. In 3 the membranes had ruptured spontaneously or artificially more than 48 hours before labor began, so that, despite the absence of obvious maternal pyrexia, some intrauterine infection cannot be excluded.

Cord Entanglement.—In 86 cases of this series fetal distress was considered due to cord entanglement or prolapse. There were 10 babies lost and in almost all fatal cases meconium staining was present alone or in combination with slowing of the fetal heartbeat.

Of 29 cases of fetal distress with meconium staining which occurred *in the first stage of labor* before the end of the fortieth week, 11 were caused by cord complications. In the forty-first and later weeks the figures are 113 and 23, respectively, i.e., cord complications are likely to be responsible for meconium staining early in labor in about one third of cases before term and one fifth after.

Conclusions

What then are the lessons we can learn?

1. That fetal distress is, in our community, relatively common and carries a fairly high mortality.

2. That because of our present attitude, which considers fetal heart slowing a relatively dangerous sign, indicating interference and delivery, we lose very few babies in such cases.

3. That because we have been unwilling to accept meconium staining and fetal heart rapidity as dangerous signs we may lose more babies than we should. This agreed with the conclusions of Resnick[45] and Lister and Buchanan.[29]

Meconium.—I would not advocate immediate cesarean section on this indication alone except when it is seen before or early in labor in the case of a primigravida over 30 years of age. Meconium sometimes follows the use of Pitocin, quinine, or castor oil in medical induction. In such cases it is "old" and lightly stains the liquor. All such cases are excluded from the oxygen series. Such drugs were rarely used in our cases.

I feel that when meconium first appears in a prolonged labor, e.g., over 24 hours, the mother should be given oxygen and the case assessed. If labor is likely to last many more hours, delivery by cesarean section is strongly indicated.

When it is associated with accidental hemorrhage and pre-eclampsia, it is particularly dangerous.

Rapid Heartbeat.—Rapidity of the fetal heartbeat is seen in labor in the presence of some maternal infection, or often in labor after the membranes

have been ruptured for many days even in the absence of maternal pyrexia. It may also be seen when labor is prolonged. If associated with meconium, the need for delivery appears to be urgent. Alone and with maternal pyrexia it will presage fetal death from infection unless suitable measures are taken.[50]

Sequelae.—It is impossible to ignore the strong possibility that many of of the babies who survive despite distress are permanently damaged. This paper serves to show the incidence of distress in various groups, to emphasize the likely size of the problem and to point the way for future study. I have made many assumptions about likely oxygen levels in the carotid vessels but these cannot be far out and only future study will solve these problems.

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References

1. Acheson, G. H., Dawes, G. S., and Mott, J. C.: J. Physiol. **135**: 623, 1957.
2. Barclay, A. E., Franklin, K. S., and Pritchard, M. M. L.: Foetal Circulation, Oxford, 1946, Blackwell Scientific Publications.
3. Barcroft, J.: Researches in Prenatal Life, Oxford, 1946, Blackwell Scientific Publications.
4. Barcroft, J., Kennedy, S. A., and Mason, M. F.: J. Physiol. **97**: 347, 1939.
5. Barron, D. H., and Meschia, G.: Cold Spring Harbor Symposium on Quant. Biol. **19**: 93, 1954.
6. Bartels, H.: Proc. C.I.O.M.S., Josiah Macy, Jr., Symposium, Oxford, 1959, Blackwell Scientific Publications. (In press.)
7. Bartholomew, R. A.: Am. J. Obst. & Gynec. **10**: 89, 1925.
8. Bernard, R. M.: Trans. Obst. Soc. Edinburgh **104**: 1, 1952.
9. Browne, J. C. McClure: In Oxygen Supply to the Human Foetus, Proc. C.I.O.M.S., Josiah Macy, Jr., Symposium, Oxford, 1959, Blackwell Scientific Publications. (In press.)
10. Caldeyro-Barcia, R., and Alvarez, H.: Physiology of Prematurity, Trans. First Conference, Josiah Macy, Jr., Foundation, 1956, p. 128.
11. Carey, H. M.: La Prophylaxie en gynécologie et obstétrique, Geneva, 1954, Georg et Cie, p. 1042.
12. Clayton, C. G., Farmer, F. T., and Johnston, T.: Lancet **2**: 2539, 1956.
13. Clemetson, C. A. B., and Churchman, J.: J. Obst. & Gynaec. Brit. Emp. **60**: 335, 1953.
14. Cox, L. W., and Chalmers, T. A.: J. Obst. & Gynaec. Brit. Emp. **60**: 203, 1953.
15. Cross, K. W., Tizard, J. P. M., and Trythall, D. A. H.: J. Physiol. **129**: 69, 1955.
16. Dawes, G. S.: Personal communication, 1957.
17. Dawes, G., Mott, J., and Widdicombe, J. G.: J. Physiol. **126**: 563, 1954.
18. Eastman, N. J.: Bull. Johns Hopkins Hosp. **47**: 221, 1930.
19. Eastman, N. J.: Bull. Johns Hopkins Hosp. **50**: 39, 1932.
20. Eastman, N. J.: Am. J. Dis. Child. **76**: 661, 1948.
21. Flexner, L. B., Cowie, D. B., Hellman, L. M., Wild, W. S., and Vosburgh, G. J.: Am. J. Obst. & Gynec. **55**: 469, 1948.
22. Guilhelm, B., Pontonnier, A., Baux R., and Bennet, P.: Gynéc. et obst. **51**: 409, 1952.
23. Haselhorst, G., and Stromberger, K.: Ztschr. Geburtsh u. Gynäk. **98**: 49, 1930.
24. Hellman, L. M.: New York J. Med. **56**: 691, 1956.
25. Hendricks, C. H.: Am. J. Obst. & Gynec. **73**: 492, 1957.
26. Hohn, E.: Personal communication, 1957.
27. Kergeradec, Lejumau H. S. A.: Mémoire sur l'ausculation appliqué à l'étude de la grosseuse, Paris, 1822.
28. King, E. L.: Am. J. Obst. & Gynec. **39**: 529, 1940.
29. Lister, U. M., and Buchanan, M. F. G.: J. Obst. & Gynaec. Brit. Emp. **64**: 233, 1957.
30. Little, W. J.: Trans. Obst. Soc., London, **3**: 293, 1862.
31. Lund, C. J.: Am. J. Obst. & Gynec. **40**: 946, 1940.
32. Lund, C. J.: Am. J. Obst. & Gynec. **45**: 636, 1943.
33. Lind, J., and Wegelius, C.: Cold Spring Harbor Symposium on Quant. Biol. **19**: 109, 1954.
34. McKay, R. B.: J. Obst. & Gynaec. Brit. Emp. **64**: 185, 1957.

35. McCance, R. A., and Widdowson, E. M.: Cold Spring Harbor Symposium on Quant. Biol. **19**: 161, 1954.
36. McKinney, L. G., Ehrlich, F. E., and Chase, H. C.: Am. J. Pub. Health **45**: 653, 1955.
37. McKinney, L. G., Goldberg, I. D., Ehrlich, F. E., Freyman, K. C.: Pediatrics **21**: 555, 1958.
38. Mayor, F. L.: Bibliothèque Universalle de Genève, 1818.
39. Minkowski, A., Cailebotte, N., Saint Anne-Dargaissies, S., Larroche, J. C., Barab, R., and Maille, G.: Neonatal Studies **2**: 197, 1953.
40. Minkowski, A.: Ann. paediat. Fenniae **3**: Fasc. 2, 1957.
41. Moore, P. T., and Myerscough, P. R.: J. Obst. & Gynaec. Brit. Emp. **64**: 207, 1957.
42. Morris, N., Osborn, S. B., Wright, H. P., and Hart, A.: Lancet **2**: 481, 1956.
43. Piraux, P.: Bull. Soc. roy. belge gynéc. et d'obst. **26**: 104, 1955.
44. Prystowsky, H.: Bull. Johns Hopkins Hosp. **101**: 48, 1957.
45. Resnick, L.: African M. J. **29**: 857, 1955.
46. Rooth, G., and Sjostedt, S.: Acta obst. et gynaec. scandinav. **34**: 442, 1955.
47. Rooth, G., and Sjostedt, S.: Arch. Dis. Child. **32**: 91, 1957.
48. Rooth, G., and Sjostedt, S.: Acta obst. et gynaec. scandinav. **36**: 374, 1957.
49. Schwartz, H.: Die Vorzeitigen Athembewegungen, Leipzig, 1858.
50. Smith, J. A. McC., Jennison, R. F., and Langley, F. A.: Lancet **2**: 903, 1956.
51. Sureau, Cl.: Gynéc. et obst. **55**: 21, 1956.
52. Taylor, H. C.: Yale J. Biol. Med. **25**: 525, 1953.
53. Taylor, E. S., Govan, C. D., and Scott, W. C.: Am. J. Obst. & Gynec. **61**: 840, 1951.
54. Turnbull, E. P. N., and Baird, D.: Brit. M. J. **2**: 1021, 1957.
55. Turnbull, E. P. N., and Walker, J.: J. Obst. & Gynaec. Brit. Emp. **63**: 553, 1956.
56. von Winkel, H.: Handb. de Geburtshülfe, Jena, 1903.
57. Walker, J.: Anoxia of the Newborn Infant, Oxford, 1953, Blackwell Scientific Publications, p. 158.
58. Walker, J.: J. Obst. & Gynaec. Brit. Emp. **61**: 162, 1954.
59. Walker, J.: Lecture in Scientile Basis of Medicine Series, Athlone Press, London, 1955-1956, vol. **5**.
60. Walker, J.: Am. J. Obst. & Gynec. (In press.)
61. Walker, J.: In Oxygen Supply to the Human Foetus, Proc. C.I.O.M.S., Josiah Macy, Jr., Symposium, Oxford, 1959, Blackwell Scientific Publications.
62. Walker, J., and Turnbull, E. P. N.: Lancet **2**: 312, 1953.
63. Watts, J., Henderson, H., Kaump, D. H., and Davis, R. M.: Am. J. Obst. & Gynec. **61**: 1025, 1951.
64. Westin, B.: Acta paediat. **46**: 117, 1957.
65. Windle, W. F.: Personal communication, 1957.
66. Yagi, H.: La Prophylaxie en gynécologie et obstetrique, Geneva, 1954, Georg et Cie, p. 1150.

PROLAPSE OF THE UMBILICAL CORD*

M. Leon Tancer, M.D., and Henry Reuss, M.D., New York, N. Y.

(From the Department of Obstetrics, the French Hospital)

PROLAPSE of the umbilical cord is a major cause of intrapartum fetal death, responsible for 20 per cent of such deaths at the French Hospital from 1935 to 1956. Compression of the cord by the presenting part results in fetal anoxia, followed by death. Several authors[1-5] have recommended a conservative plan of management in patients with prolapse of the cord, particularly in the presence of breech presentation.[6, 7] Others have recommended the earlier and more frequent use of cesarean section.[8-10] There is no unanimity of opinion.

The cases of prolapsed cord which occurred at the French Hospital have been reviewed. Two questions have been raised, the answers to which, it is hoped, will assist in the decrease of fetal wastage from this cause: (1) Should variations of the presenting part, namely, shoulder, breech, or vertex, alter the management of labor? (2) When and how should delivery be accomplished?

Material

There were 76 cases of prolapsed cord in 28,908 deliveries at the French Hospital from May, 1935, to January, 1958, an incidence of one in every 380 deliveries (Table I). Cases diagnosed as occult cord prolapse were not included. There were 35 fetal deaths, a gross mortality rate of 46.1 per cent. Three fetuses weighed less than 1,000 grams. One fetus died during the antepartum period as a result of hydrops fetalis. One fetus died during the antepartum period as a result of abruptio placenta. The remaining 71 cases form the basis of this report. In each case the patient began labor with a living fetus. There were 30 fetal deaths, a corrected fetal mortality rate of 42.3 per cent (Table II).

Table I. Incidence of Prolapsed Cord Relative to Presentation

Presentation	No. of prolapsed cords	Total no. of cases	% of all prolapsed cords	Incidence
Shoulder	4	60	5.6	1:15
Breech	29	1,091	40.8	1:38
Vertex	38	27,757	53.5	1:730
Total	71	28,908	100	1:407

The term *prompt delivery* as used in this report refers to a delivery accomplished vaginally as soon as possible after discovery of prolapse of the

*Read by Dr. Reuss at the Residents' Meeting, the Section on Obstetrics and Gynecology of the New York Academy of Medicine, May 27, 1958.

cord, such discovery having been made while the fetus was alive and the cervix fully dilatable; or by cesarean section when the cervix was not fully dilatable.

The term *delayed delivery* refers to delivery accomplished subsequent to an expectant plan of management in labor, if cord prolapse was discovered after fetal death had occurred, or if vaginal delivery was attempted prior to deliverability.

TABLE II. PERINATAL MORTALITY RELATIVE TO PRESENTATION AND TIME OF DELIVERY

PRESENTATION	PROMPT DELIVERY		DELAYED DELIVERY		TOTAL		PERINATAL MORTALITY RATE
	LIVED	DIED	LIVED	DIED	LIVED	DIED	
Shoulder	1	0	0	3	1	3	75.0%
Breech	20	2	0	7	20	9	31.0%
Vertex	20	3	0	15	20	18	47.3%
Total	41	5	0	25	41	30	
Perinatal mortality rate	10.9%		100%		42.3%		

Relation of Fetal Loss to Presentation

Shoulder Presentation.—Prolapsed cord occurred in 4 patients with transverse lie. These represent 5.6 per cent of all prolapsed cords. There were 60 patients with transverse lie so that the incidence is one prolapsed cord in 15 shoulder presentations. There were 3 fetal deaths, a mortality rate of 75 per cent.

Prolapse of the cord was discovered when the patient was deliverable and the fetus was alive in one case. Version and breech extraction were performed promptly and the infant lived. Prolapse of the cord was discovered prior to deliverability in 3 cases. Labor was permitted to continue and version and breech extraction were performed. All 3 infants were stillborn.

The presenting part in shoulder presentation is softer than the breech or vertex, and it does not fill the pelvis. Nevertheless, fetal loss was 100 per cent (3 infants) when the normal course of labor was permitted.

Breech Presentation.—Prolapsed cord occurred in 29 patients with breech presentation. These represent 40.8 per cent of all prolapsed cords. There were 1,091 breech presentations so that the incidence is one prolapsed cord in every 38 breech presentations. There were 9 fetal deaths, a mortality rate of 31.0 per cent.

Cord prolapse was discovered when the patient was considered deliverable and the fetus was alive in 16 cases. Breech extraction was performed promptly in each one. Fifteen infants were born alive; one of these weighing 1,150 grams died of prematurity in the neonatal period. One infant, the first of locked twins, was stillborn.

Cord prolapse was discovered prior to deliverability in 13 cases. Cesarean section was performed promptly in 6 cases and all infants lived. In the remaining 7 cases, all breech deliveries, the infants were stillborn.

A presenting breech does not fill the pelvis as well as a vertex. Nevertheless, fetal loss was 100 per cent (7 infants) when prompt delivery was not performed. The fetal loss was 9.0 per cent (2 of 22 infants) when delivery was accomplished promptly after discovery of cord prolapse.

Vertex Presentation.—Prolapsed cord occurred in 38 patients with vertex presentation. These represent 53.5 per cent of all prolapsed cords. There were 27,757 vertex presentations so that the incidence is one prolapsed cord in every 730 vertex presentations. There were 18 fetal deaths, a mortality rate of 47.3 per cent.

Cord prolapse was discovered when the patient was considered deliverable and the fetus was alive in 19 cases. Vertex delivery was accomplished promptly in 14 patients and there was one fetal death. Version and breech extraction were promptly performed in 5 patients and there were 2 fetal deaths, both resulting from intracranial injury.

Cord prolapse was discovered prior to deliverability in 19 patients. Cesarean section was performed promptly in 4 cases and all infants survived. Management in the remaining 15 cases included the use of Trendelenburg and knee-chest positions to relieve cord compression, oxygen given by mask, attempts to reposit the cord, and the use of a Voorhees bag. Vaginal delivery was subsequently performed in 14 cases with 14 fetal deaths. Cesarean section was performed in one case after the fetal heart tones had disappeared, because of cephalopelvic disproportion.

The vertex is firm and fits the pelvis tightly. Cord compression occurred despite physical attempts to avoid it when labor was permitted to continue. Efforts to replace the cord were equally futile. Fetal loss was 100 per cent (15 infants) when labor was permitted to continued. Fetal loss was 13.0 per cent (3 of 23 infants) when delivery was accomplished promptly after discovery of cord prolapse.

In summary, when the fetus was alive at the time of discovery of prolapse of the cord, and when delivery was accomplished promptly, the fetal mortality rates for transverse, breech, and vertex presentations were, respectively, 0.0, 9.0, and 13.0 per cent. When labor was permitted to run its course, the fetal mortality rate was 100 per cent in each group. The management of labor should not, then, be related to the presenting part. Labor should be terminated promptly, regardless of the presentation, in order to diminish fetal loss.

Relation of Fetal Loss to Type of Delivery

Version and Breech Extraction.—Ten patients were delivered by version and breech extraction. Six were delivered promptly with 2 fetal deaths due to intracranial injury. There were 4 delayed deliveries with 4 fetal deaths.

Breech Delivery.—There were 23 breech deliveries. Sixteen patients were delivered promptly with 2 fetal deaths. There were 7 delayed deliveries with 7 fetal deaths.

Vertex Delivery.—There were 27 patients delivered by a variety of vertex maneuvers. Fourteen were delivered promptly with one fetal death. There were 13 delayed deliveries with 13 fetal deaths.

Cesarean Section.—There were 11 cesarean sections. Ten were performed promptly with no fetal loss. There was one delayed cesarean with fetal death.

In summary, the method of delivery was not as important as the time of delivery. Fetal salvage was increased by nontraumatic delivery accomplished promptly after the discovery of cord prolapse. Such delivery was best accomplished by cesarean section unless conditions were such that a breech extraction or vertex delivery could safely be performed. Version and breech extraction increased fetal loss.

Relation of Fetal Loss to Interval Between Discovery of Cord Prolapse and Delivery

Less Than 10 Minutes.—Delivery occurred within 10 minutes of the time that cord prolapse was discovered in 28 cases. Fetal death had occurred prior to discovery of cord prolapse in 6. Of the remaining 22 infants, 20 survived. The death of one infant was due to intracranial injury following version and breech extraction. The other death occurred in the neonatal period because of prematurity.

10-20 Minutes.—This group includes 14 cases, in one of which fetal death occurred prior to discovery of cord prolapse. Of the remaining 13 infants, 9 survived. There were 4 fetal deaths, all as a result of trauma. Accouchement forcé and a high midforceps delivery caused one death, while breech extraction through an incompletely dilated cervix caused the other 3.

20-30 Minutes.—This group includes 4 cases with 2 fetal deaths. One resulted from a traumatic breech extraction performed through an incompletely dilated cervix. The other occurred in the first of locked twins.

30-60 Minutes.—This group includes 7 cases in one of which the fetus was dead at the time cord prolapse was discovered. In the remaining 6 cases, 2 infants delivered by cesarean section lived, while 4 patients were treated expectantly. All 4 infants died before deliverability occurred.

60 Minutes Plus.—There were 18 cases in this group, in 2 of which the fetus was dead prior to discovery of cord prolapse. Of the remaining 16, 8 were delivered by cesarean section and all lived. There were 8 fetal deaths following an expectant plan of management.

In summary, there were 61 infants alive at the time prolapse of the cord was discovered. Thirty-nine patients were delivered in less than 30 minutes and 31 infants survived. Of the 8 deaths, 6 resulted from traumatic delivery through an incompletely dilated cervix. Twenty-two patients were delivered more than 30 minutes after cord prolapse was discovered and 10 infants, all delivered by cesarean section, lived. Twelve cases were managed expectantly and resulted in 12 fetal deaths. Nontraumatic delivery, performed within 30 minutes of the time cord prolapse was discovered, increased fetal salvage. Attempts to rush vaginal delivery through an incompletely dilated cervix were disastrous, and an expectant plan for the management of labor was equally so. Cesarean section in patients not at the time deliverable from below prevented fetal loss.

Diagnosis

The need for diagnosis before fetal death occurs is obvious. Some authors[1, 11] feel that signs of fetal distress will alert the attendant to the possible presence of a prolapsed cord. In this series, however, signs of distress were noted prior to the discovery of cord prolapse in only 19.7 per cent of the cases. There were fetal heart changes in 12 cases and meconium was present in 2 of 38 vertex presentations. Also, there were 10 cases in which fetal death occurred prior to the discovery of cord prolapse, and in none of these were distress signs noted, despite the fact that labor room attendants in our hospital are conscientious and well trained. Unfortunately, vaginal examinations were not performed in the latter cases until after fetal heart tones had disappeared.

Vaginal examinations should be used more frequently to follow the progress of labor, particularly in transverse, breech, and unengaged vertex presentations.

In addition, the time when spontaneous rupture of the membranes occurred was known in 59 of 71 cases. The interval between the time of rupture and the discovery of cord prolapse averaged 3 hours and 34 minutes. It appears obvious that this interval could be shortened considerably if a vaginal examination were to be performed immediately after rupture of the membranes.

Cesarean Section

We agree with Cox[9] that cesarean section should be performed when prolapse of the cord is discovered before the patient is safely deliverable from below. Unfortunately, there may be a delay of 30 to 90 minutes while the operating room is being prepared. Eastman[12] has suggested, and we have used, spinal anesthesia in order to halt labor during this time.

Immediately after the diagnosis of prolapsed cord is made, 8 mg. of hyperbaric Pontocaine is given intrathecally via the fourth lumbar interspace. Labor stops, and fetal heart tones, if irregular, return to normal. Cesarean section may then be performed up to 75 minutes later. When necessary, supplementary intravenous or inhalation anesthesia may be used to complete the operation after delivery of the infant.

Summary

1. Prolapse of the cord was associated in this series with a corrected perinatal mortality rate of 42.3 per cent. Among the infants delivered promptly, per vaginam when this was safe, and by cesarean section when vaginal delivery was unsafe, the mortality rate was 10.9 per cent. When an expectant plan of management was followed, the mortality rate was 100 per cent regardless of presentation. Cesarean section should be performed unless prompt vaginal delivery can safely be accomplished.

2. Cord prolapse was suspected as a result of fetal distress in only 19.7 per cent of cases. Early diagnosis is best accomplished when vaginal examination is used to follow progress in labor, particularly in shoulder, breech, and unengaged vertex presentations. Vaginal examination should be carried out immediately on rupture of the membranes.

3. Spinal anesthesia should be used to halt labor when preparations for cesarean section are expected to delay delivery. The use of Trendelenburg or the knee-chest position, and attempts to reposit the prolapsed cord, were futile when labor was permitted to continue.

References

1. Cope, E.: J. Obst. & Gynaec. Brit. Emp. **58**: 259, 1951.
2. Brandeberry, K. R., and Kistner, R. W.: AM. J. OBST. & GYNEC. **61**: 356, 1951.
3. Bourgeois, G. A.: AM. J. OBST. & GYNEC. **41**: 837, 1941.
4. Slate, W. G., and Randall, J. H.: AM. J. OBST. & GYNEC. **72**: 991, 1956.
5. Mengert, W. E., and Longwell, F. H.: AM. J. OBST. & GYNEC. **40**: 79, 1940.
6. Braye, M., and Colette, C.: Rev. franç. de gynéc. et d'obst. **52**: 371, 1957.
7. Greenhill, J. P.: Obstetrics, ed. 11, Philadelphia, 1955, W. B. Saunders Company, p. 678.
8. du Toit, P. F. M.: South African M. J. **30**: 1181, 1956.
9. Cox, L. W.: Lancet **1**: 561, 1951.
10. Kush, A. W.: AM. J. OBST. & GYNEC. **66**: 182, 1953.
11. Titus, Paul, and Willson, J. R.: The Management of Obstetric Difficulties, ed. 5, St. Louis, 1955, The C. V. Mosby Company, p. 668.
12. Eastman, N. J.: Williams Obstetrics, ed. 11, New York, 1956, Appleton-Century-Crofts, Inc., p. 882.

1 EAST 68TH STREET
NEW YORK 21, N. Y.

THE RELATIVE EFFECTS OF OBSTETRICAL ANESTHESIA AND ANALGESIA UPON THE PROMPTNESS OF NEONATAL RESPIRATION

KENNETH G. PHILLIPS, M.D., TORONTO, ONT.

(From the Boston Lying-in Hospital and the Department of Pediatrics, Harvard Medical School)

ATTEMPTS[1, 2] have been made to assess the respective contributions of preanesthetic medication and of general anesthesia to disturbance of respiration in the newborn infant. Nevertheless, doubt remains as to which of these two general groups of pain-relieving agents is of primary importance in causing delay in breathing. Obviously, if used in excessive dosage, either the medication or the general anesthetic will disturb the infant's responsiveness. Moreover, each undoubtedly supplements the effect of the other. But since progress depends upon attacking the major offender, its identity becomes of some importance.

In the study here reported, a large series of infants delivered under spinal anesthesia were analyzed for sedative effects which were presumably caused by the analgesic medication alone.

Method

Infants born to two groups of private patients at the Boston Lying-in Hospital were observed.* Those of the first group were delivered under spinal anesthesia by an obstetrician† accustomed to that method and employing it in all cases except those with technical difficulties or unsuitably rapid labors. The usual spinal anesthetic was procaine hydrochloride in doses of 40 to 100 mg.; occasional patients were delivered under intrathecal Pontocaine, 5 to 30 mg. Almost all received from 25 to 100 mg. of ephedrine sulfate intramuscularly at the time of administration of the anesthetic. Delivery usually occurred within 45 minutes after the mother was anesthetized. The second group consisted of patients who were delivered by other staff obstetricians under inhalation anesthesia. The agents were nitrous oxide plus oxygen plus ether in 89 per cent, oxygen plus ether in 8.5 per cent, and nitrous oxide-oxygen in 2.5 per cent of the cases.

Although spinal anesthesia was considered to be essentially the equivalent of no anesthesia at all in its effects on the baby, an ideal investigation would obviously have included two subgroups of deliveries under spinal—one with, and one without analgesic premedication—and two comparable subgroups of generally anesthetized patients also delivered with and without premedication. Actually, since current obstetrical practice in this hospital[3]

*These observations were made before the establishment of the full-time anesthesia service at that hospital.

†The late Dr. Paul Gustafson, whose interest and assistance are gratefully recorded.

accepts premedication as more or less essential in labor, almost all women in both major groups received analgesic drugs. This, nevertheless, offered the possibility of evaluating the effects of such drugs *per se* on the infants of mothers delivered under spinal anesthesia, and of assessing effects which might be contributed by general anesthesia as indicated by any disproportionate modification of postnatal activity in infants whose mothers received general anesthetics after their analgesic premedication.

The analgesic agents used before both types of anesthesia were more or less similar. Almost every patient received a barbiturate (sodium pentobarbital or Seconal) with scopolamine, and about a third of each group received Demerol as well. A few women in each group received Pantopon.

In each case the infant's respiration was recorded as *prompt* if the spontaneous onset of breathing occurred within one minute after delivery, and if there was no more than the usual transient cyanosis and no mucus in the upper respiratory tract. Otherwise the respiration was recorded as *delayed*. The time required for the onset of respiration was measured by Dr. Gustafson in the deliveries under spinal anesthesia, and by the delivery room supervisor in those under inhalation anesthetic.

The cases were successive and unselected in both groups, except that deliveries with conditions not related to the analgesia or anesthesia but which might adversely affect respiration were excluded. These were cases in which: (1) the fetal presentation was other than vertex, (2) the delivery was other than spontaneous or by low forceps, (3) the duration of labor was more than 20 hours, (4) labor was complicated by prolapse of the cord or premature separation of the placenta, (5) there were marked abnormalities of the fetus, or (6) the infant's birth weight was less than 5 pounds.

This resulted in a comparable distribution in the two groups as to maternal age, parity, and other obstetrical factors.

Results

Table I shows the relative incidence of delayed respiration to have been almost six times as great in the general as in the spinal anesthesia group. Statistically, this result is significant on the basis of a chi-square test. It is therefore clear that the inhalation anesthetics used affected the activity of the newborn infant.

TABLE I. RELATIVE INCIDENCE OF PROMPT RESPIRATION AND TYPE OF ANESTHESIA

ANESTHESIA	PROMPT RESPIRATION		DELAYED RESPIRATION		TOTAL
	NO.	%	NO.	%	
Spinal	741	96.9	24	3.1	765
General	375	82.1	82	17.9	457

Table II presents data as to the analgesic agents employed before anesthesia. Scopolamine, which was almost always given with the barbiturates, was used in comparatively small doses, below the level which might affect infant respiration, and it is therefore omitted from the table. Barbiturates were used in the great majority of labors, regardless of the type of anesthetic. There is thus no apparent way of determining whether this medication of itself was influential in delaying the onset of respiration except on the premise stated above that spinal anesthesia is equivalent to no anesthesia. Thus, the fact that prompt respiration occurred so consistently after barbiturates and spinal anesthesia seems to indicate that the barbiturate medication in these doses was of little effect upon the onset of respiration.

TABLE II. ANALGESIC AGENTS EMPLOYED BEFORE ANESTHESIA

ANALGESIC AGENTS	GROUP 1. SPINAL ANESTHESIA						GROUP 2. INHALATION ANESTHESIA					
	PROMPT RESPIRATION			DELAYED RESPIRATION			PROMPT RESPIRATION			DELAYED RESPIRATION		
	(1) NO. OF CASES	(2) %	(3) AV. DOSE	(4) NO. OF CASES	(5) %	(6) AV. DOSE	(7) NO. OF CASES	(8) %	(9) AV. DOSE	(10) NO. OF CASES	(11) %	(12) AV. DOSE
Total Cases	741	100		24	100		375	100		82	100	
Barbiturate.—												
No. of cases	731	98.6	6.9 gr.	20	83.4	9.8 gr.	364	97.1	7.5 gr.	77	93.9	8.3 gr.
Within 4 hours ante partum	585	79.0	4.0 gr.	20	83.4	4.0 gr.	306	81.7	4.9 gr.	58	70.8	4.4 gr.
Demerol.—												
No. of cases	286	38.6	112 mg.	7	29.1	200 mg.	79	21.1	97 mg.	30	36.6	113 mg.
Within 4 hours ante partum	115	15.5	81 mg.	3	12.5	100 mg.	62	16.5	80 mg.	21	25.6	95 mg.
Barbiturate and Demerol.—												
No. of cases	280	37.8		7	29.1		66	17.6		30	36.6	
Within 4 hours ante partum	96	13.0	3.5 gr. barbiturate 88 mg. Demerol	2	8.3	4.5 gr. barbiturate 100 mg. Demerol	40	10.7	4.1 gr. barbiturate 75 mg. Demerol	14	17.1	5.8 gr. barbiturate 82 mg. Demerol
Barbiturate Without Demerol.—												
Within 4 hours ante partum	489	66.0		18	75.0		266	71.9		36	43.9	

TABLE III. COMPARISON OF THE INFLUENCE OF ANESTHETIC AND ANALGESIC AGENTS

TOTAL NO. OF INFANTS	ANALGESIC BEFORE EITHER TYPE OF ANESTHESIA						ANESTHESIA AFTER ANY TYPE OF ANALGESIA			
	DEMEROL			BARBITURATE			GENERAL		SPINAL	
	NO. OF INFANTS	PER CENT OF A OR B	AV. DOSE	NO. OF INFANTS	PER CENT OF A OR B	AV. DOSE	NO. OF INFANTS	PER CENT OF A OR B	NO. OF INFANTS	PER CENT OF A OR B
A. 1,116 with prompt respiration	365	32.7	109 mg.	1,095	98	7.1 mg.	375	33.6	741	66.4
B. 106 with delayed respiration	37	34.9	129 mg.	97	91.5	8.6 mg.	82	77.3	24	22.7

It will be noted from the second column of Table II that more than 98 per cent of all the deliveries under spinal anesthesia resulted in infants who breathed promptly followed barbiturate medication. In column 5 it appears that in a smaller percentage (83.4 per cent) of the infants whose respiration was delayed after delivery under spinal anesthesia barbiturate medication had been used. A similar relationship appears in columns 8 and 11, for barbiturate usage before inhalation anesthesia. These trends are just the reverse of what would be anticipated if the medication had been the significant factor affecting the infant's activity.

It is of interest that a comparison of columns 3 and 5 does show a larger average barbiturate dose used in the 20 deliveries producing the less active infants, whereas the difference between average doses of 7.5 and 8.3 grains of barbiturates in columns 9 and 12 is relatively small.

This suggests that if inhalation anesthesia is not used, only a rather large dose of analgesic medication will contribute to delayed respiration, whereas inhalation anesthesia may of itself affect neonatal respiration more significantly than do the barbiturates used before it.

Demerol was used before a considerably smaller number of deliveries under either spinal or inhalation anesthesia than were the barbiturates. Again, infants with slow onset of respiration were born to mothers who received, on the average, more Demerol than was administered to the mothers of infants with prompt respiration. Also, the difference in Demerol dosage was again much greater (200 mg. vs. 112 mg.) in the infants with delayed and prompt respiration born under spinal anesthesia. If given in moderate doses, this form of analgesia, like the barbiturates, appears to be of less effect in retarding the onset of respiration than a general anesthetic given to the mother.

As only two mothers received Pantopon within 4 hours prior to delivery these figures have been omitted.

If the data are analyzed, as in Table III, in an attempt to demonstrate whether administration of analgesia during labor or employment of general anesthesia during delivery is the primary factor affecting respiratory onset, the evidence clearly indicates the greater importance of the anesthesia. This is, of course, obvious from the previous table. Of the two analgesics selected for analysis in Table III, the figures suggest a slight tendency for Demerol to contribute to poor respiration, but no tendency for barbiturates to do so. These differences are too small to be of significance.

Summary and Conclusions

A comparison of 765 infants delivered under spinal anesthesia with 457 delivered under general anesthesia clearly indicates that respiration is more prompt and efficient after spinal than after general anesthesia. Under the circumstances of this study the factor of anesthesia for delivery appears to be more significant in delaying neonatal respiration than the sedative action of analgesic drugs given during labor.

Since the difference in onset of respiration upon which this study is based is not known to affect the infant, the results of the study are not intended, by themselves, to decide the choice of the anesthetic in labor. It is realized that there are many factors, other than those considered here, which will influence

that choice. This is merely an attempt to evaluate the relative effect of analgesic and anesthetic agents on the onset of respiration in the newborn infant.

This study was done under the direction of Dr. Clement A. Smith.

References

1. Smith, C. A.: In Levine, S. Z., Butler, A. M., Holt, L. E., Jr., and Weech, A. A., editors: Advances in Pediatrics, New York, 1948, Interscience Publishers, Inc., vol. III, p. 1.
2. Snyder, Franklin F.: Obstetric Analgesia and Anesthesia, Philadelphia, 1949, W. B. Saunders Company.
3. Hershenson, B. B.: New England J. Med. 239: 429, 1948.

SOME CONSIDERATIONS OF EXCESSIVE FETAL DEVELOPMENT

A Study of 144 Cases

RICHARD N. BOLTON, M.D., PORTLAND, ORE.

(From the Department of Obstetrics and Gynecology, University of Oregon Medical School)

WE EXPECT the majority of deliveries involving infants of 4,500 grams or more to terminate happily and uneventfully. This is not always the case, however. There are many who well remember the "adequate multipara" who was delivered abdominally after a prolonged labor because the diagnosis of excessive development or borderline pelvic contraction was not made. In emphasizing the external conjugate, Eastman[5] stated, "The number of women who have been allowed to suffer hours of hopelessly obstructed labor because this dimension was normal are legion." He might well have been speaking of the women with an "average" pelvis and large fetus. All too frequently, theirs is the same plight.

It is difficult to judge the size of a fetus in utero, yet, as Neilson and Neilson[15] stated, "The experienced obstetrician can usually think in terms of small, average, and large babies"; and must do so if these cases are to be suspected. The concept of the pelvis as a static passage and the fetus as a somewhat unpredictable passenger becomes most important when the child is larger than usual.

This study is presented to increase our index of suspicion so that the possibility of excess development may be entertained before difficulty with delivery has occurred.

With this in mind, it is worth while to review the experience with the delivery of excessively developed infants at the University of Oregon Medical School, Portland, Oregon.

Material and Incidence

All infants weighing 4,500 grams or over delivered in the Multnomah Hospital unit of the University of Oregon Medical School Hospitals and Clinics from 1946 through 1956 are included. These were all clinic patients.

During this period there were 8,973 deliveries, 144 of which constitute the material of this study. Our incidence of 1.6 per cent is quite comparable to that previously reported.[11, 14]

There is a racial differential in the occurrence of excessive-sized infants. Kishimoto[10] reported 0.4 per cent in Japan; Posner and associates,[19] reporting from the Harlem Hospital, found only 0.61 per cent over 10 pounds (4,535

grams) in a 97 per cent Negro population. Negro patients accounted for 9.6 per cent of the Oregon series. Of all our patients, about 24 per cent are Negro. The difference is obvious.

Data on Mothers

There were 131 multiparas (90.2 per cent) and only 13 primiparas (9.8 per cent) in this series. This predominance of multiparas has been noted by previous authors.[11, 14, 27]

The majority were under 30 years of age, as shown in Table I, and most of the primiparas were under 25 years of age. There was a 9.2 per cent incidence of Rh-negative mothers. Fortunately, there were no complications due to Rh incompatibility. Positive serologic tests for syphilis were recorded in 4.8 per cent of our cases.

TABLE I. AGE DISTRIBUTION OF MOTHERS

	PRIMIGRAVIDAS 9.02%		MULTIGRAVIDAS 90.98%	
AGE GROUP	NO. CASES	%	NO. CASES	%
16-20	10	6.87	13	9.02
21-25	3	2.08	36	18.04
26-30	1	0.68	42	29.16
31-35	—	—	23	15.0
36-40	—	—	10	6.87
40 and over	—	—	5	3.43

Maternal Stature and Weight Gain

Hunt[7] has stated that large couples tend to have large babies. His series of mothers had an average weight of 145.2 pounds and an average height of 5 feet, 4 inches. Table II shows the height distribution of our patients. The majority ranged between 5 feet, 3 inches and 5 feet, 5 inches. However, 44.6 per cent were 5 feet, 6 inches tall and over. The average height of the American woman is about 5 feet, 4 inches.[22] The concept that sizable mothers have sizable children is valid, but is not quite the entire picture. Table III, after Nathanson,[14] gives the amount of weight gained by the mothers in this series. Almost 40 per cent gained in excess of 33 pounds and another 30 per cent gained between 24 and 33 pounds. This is an extreme weight gain and affords a point of suspicion concerning the clinical diagnosis of excessive fetal development.

TABLE II. HEIGHT OF MOTHERS

HEIGHT	NO. CASES	%
5 feet, 0 inches-5 feet, 2 inches	13	16.88
5 feet, 3 inches-5 feet, 5 inches	30	38.96
5 feet, 6 inches-5 feet, 8 inches	21	27.27
5 feet, 9 inches-up	13	16.88
Total	77	100.00

TABLE III. WEIGHT CHANGES IN MOTHERS OF EXCESSIVE INFANTS

WEIGHT CHANGES	NO. CASES	%
Loss of weight	6	4.65
No alteration	—	—
Gains of 1-24 pounds	38	29.45
Gains of 24-33 pounds	37	28.68
Gains in excess of 33 pounds	48	37.20
Total known	129	100.00

Here, one might logically ask if curtailment of maternal weight would have any influence on the fetal weight. Smith[24] studied the average weight by groups of infants born of undernourished mothers in war-time Holland. He found that all groups had a decrease in average weight, and the greatest was in large infants. He also noted a decrease in average length. Slemons and Fagan[23] studied infant birth weights and the maternal weight gain. They reported an average weight gain of 26 pounds in women who were delivered of infants of 10 pounds or over, but were doubtful that curtailing maternal weight gain would significantly reduce birth weight.

Maternal Diabetes Mellitus and Prediabetes

Diabetes has long been incriminated as a cause of large babies. Nevertheless, the actual incidence of diabetic mothers discovered by review of a series of large babies is small. Koff and Potter[11] found 2 in 195 cases; Nathanson,[14] 21 in 756; Posner and associates,[19] 12 in 547 births of infants over 9 pounds. There was one diabetic mother in the present series of 144. If one compiles the experience of these four series, however, it will be seen that there were 36 diabetic mothers in 1,642 cases: an incidence of 2.19 per cent. When this is taken into account, along with the usual occurrence of 0.2 to 0.1 per cent of all pregnant women,[5] it becomes a condition worthy of notice.

The relationship of large infants to the future development of diabetes is equally, if not more, interesting. Kriss and Futcher[12] studied the obstetrical histories of 100 diabetic and 100 nondiabetic women of the same age group. They found 144 infants over 10 pounds at birth, out of a total of 675. The startling aspect is that 77.1 per cent were born to the group of mothers who developed diabetes in subsequent years. Jackson[8] also studied the obstetrical careers of diabetic women and found that 62 per cent of them had at one time been delivered of an infant of 10 or more pounds. Paulson[18] discussed the syndrome of prediabetes and reported as an example the case of a woman whose fourth pregnancy terminated in the delivery of an 18 pound, 3¾ ounce stillborn infant. She developed clinical diabetes 5 years later. There was one such case in this series:

> This patient (Unit No. 38675), a 35-year-old gravida viii, para vii, was delivered of a 5,060 gram (11 pounds, 3 ounces) male infant in 1946. She was 5 feet, 5 inches tall and her weight was 244 pounds at the end of that pregnancy, during which she gained 16 pounds. Labor lasted 2 hours and 34 minutes; the delivery was spontaneous and without difficulty. In 1932, she was delivered of a 4,600 gram infant, and then of 6 more which were under 4,500 grams. In 1955, she developed clinical diabetes. She is now followed regularly in the Diabetes Division of the Outpatient Clinic. There have been no subsequent pregnancies.

There were 16 with family histories positive for diabetes. This represents 11.1 per cent of the series. We have no data on the incidence of family histories positive for diabetes in our general obstetrical clinic group, but would be very surprised if it is this high.

Toxemia

Toxemia of pregnancy is not a common problem on the obstetrical service of the University of Oregon Medical School, occurring in between 4 and 5 per cent of all our patients. Toxemia was present in 15.8 per cent of the pregnancies comprising this series. There was no eclampsia. Most recent series[11, 14, 19] report a marked increase in toxemia associated with excessive development as described in Table IV. Only Sylvester[27] did not find an increase in toxemia.

TABLE IV. REPORTED INCIDENCE OF TOXEMIA

AUTHOR	%
Koff and Potter[11]	27.3
Posner et al.[19]	22.5
Bolton (this series)	15.8
Nathanson[14]	10.9
Sylvester[27]	No increase

Previous Large Infants

Our data concerning previous large infants are incomplete. Nevertheless, there were 19.4 per cent who had delivered infants of 9 pounds, 15 ounces or more before the delivery included in this series. When compared with a general occurrence of about 1.7 per cent, it is obvious that a past history of excessive development should forewarn us that there is a good chance of its recurrence.

Prolongation of Pregnancy and Its Relation to Size of Fetus

We are all dissatisfied with current methods of determining the date of confinement. When Nägele's rule is used, however, it is found that very few women are delivered after 293 days of gestation. Strand[26] found that 12.4 per cent of 3,694 pregnancies were terminated after 293 days. Lindell,[13] in a similar review, held that a pregnancy continuing 2 weeks past the expected date of confinement could reasonably be considered prolonged.

Recalling these background data, it is interesting to study the length of gestation post menstruation of the infants in this series. There were 9 instances where the menstrual data were completely uncertain; these were omitted. Surprisingly, the remaining 135 claimed regular 28 to 30 day cycles, and remembered the date of the last period. Table V presents the findings. As can be seen, 58.3 per cent extended 41 weeks or longer, with 21.4 per cent 43 weeks or over. Interestingly, 18.5 per cent were delivered during the fortieth week, and 22.7 per cent before the fortieth week. Nathanson similarly found that 84.25 per cent of his patients continued beyond term. Koff and Potter[11] report 288 days as the average duration in their study of large babies. They found that 37.08 per cent were delivered after 294 days. There seems little doubt that large infants, as a group, have somewhat longer gestations than those of smaller weight groups.

TABLE V. DURATION OF PREGNANCY POST MENSTRUATION

WEEK	RANGE OF DAYS	NO. CASES	%		
37	259-265	6	4.4	22.7	
38	266-272	8	5.8		
39	273-279	17	12.5		
40	280-286	25	18.5		
41	287-293	28	20.7		58.3
42	294-300	22	16.2		
43	301-307	14	10.3	21.4	
44	308-over	15	11.1		

Labor

Table VI gives the data on the first and second stages of labor in the multiparas only. There were too few primiparas for any complete separate consideration. It is interesting to note, however, that all primiparas were delivered in less than 18 hours; 84.9 per cent of the multiparas completed the first stage in less than 12 hours, and the greater number completed the second stage in less than 30 minutes.

TABLE VI. LENGTH OF LABOR IN MULTIPARAS

	NO. CASES	PER CENT
Length of First Stage (Hours).—		
0-6	68	53.96
6-12	39	30.95
12-18	17	13.49
18-24	—	—
Over 24	2	1.58
Length of Second Stage (Minutes).—		
0-15	53	42.05
15-30	38	30.79
30-45	19	15.07
45-60	9	7.14
60-90	4	3.17
90-120	1	0.79
Over 2 hours	2	1.78

This obvious rarity of prolonged labor, especially in the multiparas, corresponds to the now generally prevalent concept that most excessive infants do not produce prolonged labor. So a prolonged labor cannot be accepted as "normal" when a large fetus is known to be present. The same tenets of management hold in the conduct of these cases as in those involving an average-sized fetus.

Method of Delivery and Mechanism

In this series, 85.4 per cent were delivered spontaneously, 6.9 per cent by forceps, and 7.6 per cent by cesarean section. Elective forceps delivery was practiced in the series. Hence, it seems more realistic to consider the vaginal deliveries in terms of "easy" and "difficult." There was 89.5 per cent classed as easy, and 10.5 per cent as difficult. In the former group, there were only 7 forceps terminations—all elective. Occiput anterior mechanisms accounted for 77.3 per cent; 16.8 per cent were occiput posterior with anterior rotation, either spontaneously or manually. There were 3.3 per cent delivered easily as occiput posterior, and 4.2 per cent were breech. All were frank breech presentations, and all were assisted. Fortuitously, there were no breech presentations in the difficult group. The causes of difficult delivery in this group are presented in Table VII. A prolonged second stage refers to one over 2 hours. Both of these were terminated by low forceps. Shoulder dystocia was the most common source of difficulty. Koff and Potter[11] reported 27 per cent of their cases as being complicated by shoulder dystocia, and, by measurement, revealed that this group had a 5 cm. greater average circumference than the normal, i.e., 39 cm. as against 34 cm.

TABLE VII. CAUSES OF DIFFICULT VAGINAL DELIVERY

CAUSES	NO. CASES	%
Shoulder dystocia	8	57
Difficult second stage	2	14
Deep transverse arrest	1	—
Persistent occiput posterior	1	—
Brow with forceps rotation	1	—
Rotation of occiput posterior-occiput anterior (Scanzoni)	1	—

There were 8 low cervical, three extraperitoneal, but no classical cesarean sections. Seven were done for cephalopelvic disproportion, and there were 4

classed as repeat cesareans. None of the patients who were delivered vaginally had had a previous cesarean section. There were two brow presentations; the rest were by vertex. All patients operated upon because of disproportion had trials of labor. The total labor before section averaged 18 hours. The infant weight in this group followed the same distribution as that in the general series. The cesarean section rate of 7.6 per cent is greater in this series than our general one of 5 per cent.

Table VIII represents the presentations of all the infants in this series. Calkins and Pearce[3] found that there tended to be an increase in bregma presentations as the fetal weights increased. Previous authors[7, 11, 14, 19, 27] have not noted this, or at least seldom mention it. There were none coded as such in our records.

TABLE VIII. PRESENTATIONS

PRESENTATION	NUMBER	%
Vertex	136	93.7
Brow	3	2.9
Breech	5	3.4

Aside from the brow presentations, the percentage of which is undoubtedly due to the size of the sample, there was a paucity of abnormal presentations.

Fetal Condition and Injury

There were 18 infants who were described as being in poor condition upon delivery. Two were transiently cyanotic and recovered with oxygen therapy. Twelve were depressed to such an extent that they required resuscitation by oxygen, caffeine, N-allylnormorphine hydrochloride,* and mild cutaneously administered physical stimuli. All recovered before leaving the delivery room. Only 2 had serious neurological injury: in one case, a transient left facial weakness following a difficult midforceps delivery of a brow presentation; in another, Erbs' paralysis on the left side. This infant weighed 6,170 grams (13 pounds, 10 ounces) and there was severe shoulder dystocia. Unfortunately, there was no sign of improvement at 1 month of age and the child was lost to this clinic after that time. There were no fractures reported in this series.

No neonatal deaths occurred. There was one stillbirth—a macerated fetus. The cause of this death is not known.

Nathanson[14] in his large series reported 12 with fractures of the shoulder girdle, and 13 with serious neurological injuries.

Blood Loss

We are all aware of the pitfalls of estimating blood loss. Still, this remains the most common method of computing the loss of blood at delivery. Calkins[1] reminds us, "One cannot emphasize too strongly the importance of both measuring and recording the amount of blood loss, as without this practice, one regards the loss as only one-third to one-half the actual figures." As far as can be told, all the statements on blood loss with the delivery of large infants in recent series were estimates. So it is with our cases. Table IX shows the number and per cent of cases in blood-loss groups. Only 5 per cent had a postpartum hemorrhage. Three of these were due to atony of the uterus; 3 were due to lacerations of the birth canal; and one was due to a partially separated placenta.

*Nalline hydrochloride, Merck Sharp & Dohme, Philadelphia, Pa.

TABLE IX. ESTIMATED BLOOD LOSS IN 133 VAGINAL DELIVERIES OF LARGE INFANTS

ESTIMATED BLOOD LOSS	NO. CASES	%
Less than 100 ml.	11	8.27
100-200 ml.	38	28.57
200-300 ml.	36	27.06
300-400 ml.	25	18.79
400-500 ml.	14	10.52
500 or more ml.	7	5.03

In one excellent analysis, Reich[20] found a direct correlation between fetal weight, placental size, and measured blood loss. If the infants weighed 9 pounds or over, there was a 25 per cent incidence of postpartum hemorrhage.

Infants

There were 73.7 per cent males and 26.3 per cent females. This is in general agreement with other studies.

The weights ranged from 4,500 to 6,360 grams. The largest weight group was 4,500 to 5,000 grams; this accounted for 83.5 per cent of the infants.

All the fetal charts were reviewed and, when available, the circumference of the head, chest, and the length were noted.

The circumference of the majority of fetal heads was between 36 and 38 cm., the smallest was 34, and the largest was 43 cm. The average circumference is 35 cm.[16] The largest group had chest measurements between 36 and 38 cm. Here, 33 was the smallest, and 39 the largest, 33 being the average fetal chest diameter.[16] Most of these infants were from 53 to 56 cm. in length. The shortest was 51, and the longest, 60 cm. The average fetal length is 50 cm.[16]

Postmaturity

Postmaturity, depending upon what one reads, will be based on gestational age, gestational age plus specific length and weight requirement,[17] the status of the skin, hydration, and alertness of the infant; or the condition is simply denied.

Alteration in the length of gestation produces large infants in increased proportion, small infants in increased proportion, and an increase in infants with abnormal skins. Clifford[4] describes 37 liveborn infants whom he diagnosed as postmature, solely on the basis of skin changes. The vast majority were subsequently found to be products of gestations of 291 days or over. Some were not, however. Strand[26] also found that the number of infants diagnosed as hypermature (postmature) on the basis of skin changes increased as gestational age increased, but reports that the majority from prolonged pregnancy were normal. Neither of these authors invokes length or weight as diagnostic criteria. Length of gestation per se is not a good diagnostic basis because many infants with the stigma of postmaturity result from normal or even shortened pregnancies. Size of the fetus, while an important variable, does not carry the high mortality and morbidity that postmaturity based on skin changes does, and hence seems a poor diagnostic point. It is said by some that postmaturity is not a problem,[2] but Clifford[4] reported a 21 per cent neonatal mortality in a series of infants with postmaturity based on skin and hydration changes.

In this series, there were 10 infants out of 144 who presented some degree of postmaturity. Six had only dry, scaling skin and 4 also had definite meconium staining. Only 2 of the 6 with dry skin alone went 2 weeks or more past the calculated dates of confinement, and were all average sized for this series. Of the 4 with staining, one was delivered 10 days early (14 pounds,

1 ounce), with a macerated scrotum and very scaling skin. The others were all 4 to 6 weeks past their respective dates of confinement, and average sized. All were "normal" at discharge in 5 days.

With the hope that this blurred clinical syndrome will eventually clear, we must quote Strand[26]: "The maturity or hypermaturity of the fetus is a biological state and is not easily defined. In practice a number of the signs consistently found in infants delivered at term are taken to be signs of maturity. Maturity or hypermaturity is therefore a developmental concept while full-term or over-term infant or pregnancy is a concept of time. These two do not always concur."

Comment

It would be helpful if there were a specific aspect of the pregnant patient that might give the diagnosis. Unfortunately, there is none.

There are rather good clues, however, which should bring excess development to mind. Multiparity in itself should warn of this possibility. Advanced maternal age has been pointed to as a cause of this same problem, but our figures show that the older obstetrical patient does not have a monopoly on the phenomenon of developing excessively large infants. When a patient gains more than 24 pounds, one should be alerted to the possibility of excessive size of the fetus. A past history of large babies is a positive finding and well worth investigation. If labor does not progress satisfactorily in a multipara with a good past obstetrical history, a large fetus must be considered as a possible cause. Prolonged labor is not "normal" when excess development is present.

Maternal diabetes will be encountered more commonly when the fetus is large. The really important thing, however, is the high rate of prediabetes in this group. It is clear that there is a positive relationship between excessive development and diabetes.

Of considerable interest in connection with prolongation of pregnancy is the question: Does the fetus continue to grow after term is passed, or is development, excessive or otherwise, virtually complete by 280 days? Calkins[2] does not feel the extent of growth after 260 days is significant in determining the ultimate size of the fetus. Lindell[13] believes that the increase in weight diminishes as gestation proceeds. It probably never stops completely, though, and some increase in weight continues even with prolonged pregnancy. Strand[26] quotes Rütte[21] as finding that weight and length increase at the same rate until 295 days of amenorrhea. From then on, the number of normal-sized infants (49-51.9 cm.) is reduced, while the number of small (below 48.9 cm.), and the number of large (over 52 cm.) is increased. Hosemann,[6] according to Strand,[26] felt that fetal weight, length, head circumference, and placental weight increase to the forty-fifth week, and then appear to decrease. He explained this by general dehydration. Strand found that the incidence of birth-weight over 4,000 grams was definitely increased if the gestation lasted beyond 280 days post menstruation.

Estimation of fetal size in utero is extremely difficult. To place much credence in estimated increments of weight increase in utero is asking too much. Dates of confinement based upon menstrual history, though tenuous, seem more concrete than weekly estimations of weight increase. Because of this, and the fact that any sizable series of deliveries will show an increase in average weight when pregnancy is prolonged, we find it hard to believe that development of the fetus stops at 280 days or before. Probably, the increase follows the usual sigmoid curve, but it does not stop; nor are we convinced that the postterm development is always insignificant. At any rate, a pregnancy continuing well past term should alert the physician to the possibility of excessive development.

There can be little doubt that these very large infants are more subject to severe injury than their smaller counterparts. The number of forceps operations necessary to complete some vaginal deliveries and the amount of force, when coupled with the serious seqelae, can leave no doubt that abdominal delivery is often far preferable in many of these instances where disproportion is present.

Many have tried to establish some absolute, or at least less variable, factor to help in the diagnosis of fetal size. Jacobs[9] reported good results in estimating fetal size, with fetal cephalometry. Snow[25] mentioned a soft-tissue technique to demonstrate an increased thickness of fetal fat, a feature he considered highly in favor of a large fetus. Wrigley[28] presented the concept that if there is a decrease in the amniotic fluid, an increase in muscle tone of the fetus can be noted, giving it a rigid posture. He felt this was in favor of a large infant. X-ray visualization of ossification centers, though of value in determining developmental age, helps little in determining fetal size. Actually, these contributions are most variable and are not the absolute diagnostic points we would like them to be.

In practice, one again comes to the conclusion that if a person will train himself to think of the fetus in terms of "small, average, and large,"[15] he will at least approach all pregnancies and labor by considering the size of the child. An early correct diagnosis will not be made unless this is contemplated. Such an appreciation is the first and most important step in preventing the fetal and maternal morbidity associated with excess development.

Summary

1. A high level of suspicion is required if the diagnosis of excess fetal development is to be made, and the associated complications averted.

2. The following factors should alert one to the possibility of excessive fetal development:

A. A large-statured multipara with a past history of babies weighing 4,500 grams or over.

B. Maternal weight gain in excess of 24 pounds over ideal nonpregnant weight.

C. Prolongation of pregnancy beyond 293 days post menstrual period.

D. Poor progress of labor in a patient with a good obstetrical history.

E. A palpably large fetus.

3. Few women who are delivered of excessively developed infants will have diabetes at the time, but an appreciable number will develop diabetes in the future.

4. When the fetus is large, labor is not usually prolonged and abnormal presentations are not common.

5. Severe injury to the fetus is more frequent with excess development. Abdominal delivery seems preferable if there is a large fetus and a difficult vaginal termination is likely.

6. Blood loss is frequently marked when the fetus is excessive and this constitutes a very real hazard to the mother. Anticipation of possible hemorrhage and the establishment of proper safeguards will do much to insure safe delivery of the mother with the large child.

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References

1. Calkins, L. A.: J. A. M. A. 101: 1128, 1933.
2. Calkins, L. A.: AM. J. OBST. & GYNEC. 56: 167, 1948.
3. Calkins, L. A., and Pearce, E. W.: AM. J. OBST. & GYNEC. 73: 288, 1957.
4. Clifford, S. H.: A. M. A. Am. J. Dis. Child. 86: 319, 1953.
5. Eastman, N. J.: Williams Obstetrics, ed. 11, New York, 1956, Appleton-Century-Crofts, Inc., pp. 299-783.
6. Hosemann, H.: Quoted by Strand, A.[26]
7. Hunt, A. B.: AM. J. OBST. & GYNEC. 64: 559, 1952.
8. Jackson, W. P. U.: Brit. M. J. 2: 690, 1952.
9. Jacobs, J. B.: AM. J. OBST. & GYNEC. 65: 897, 1953.
10. Kishimoto, S.: Jap. J. Obst. & Gynec. 20: 197, 1937.
11. Koff, A. K., and Potter, E. L.: AM. J. OBST. & GYNEC. 38: 412, 1939.
12. Kriss, J. P., and Futcher, P. H.: J. Clin. Endocrinol. 8: 380, 1948.
13. Lindell, A.: Acta obst. et gynec. scandinav. 35: 136, 1956.
14. Nathanson, J. N.: AM. J. OBST. & GYNEC. 60: 54, 1950.
15. Neilson, D. R., and Neilson, R. P.: West. J. Surg. 62: 153, 1954.
16. Nelson, W. E.: Textbook of Pediatrics, ed. 6, Philadelphia and London, 1954, W. B. Saunders Company, p. 31.
17. Nesbitt, R. E. L., Jr.: Obst. & Gynec. Surv. 10: 311, 1955.
18. Paulson, W. O.: AM. J. OBST. & GYNEC. 72: 1152, 1956.
19. Posner, A. C., Friedman, S., and Posner, L. B.: Obst. & Gynec. 5: 268, 1955.
20. Reich, A. M.: AM. J. OBST. & GYNEC. 37: 224, 1939.
21. Rütte, U.: Quoted by Strand, A.[26]
22. Sheldon, W. H.: Personal communication.
23. Slemons, J. M., and Fagan, R. H.: AM. J. OBST. & GYNEC. 14: 159, 1927.
24. Smith, C. A.: AM. J. OBST. & GYNEC. 53: 599, 1947.
25. Snow, W.: Roentgenology in Obstetrics and Gynecology, ed. 2, Springfield, Ill., 1952, Charles C Thomas, p. 158.
26. Strand, A.: Acta obst. et gynec. 35: 76, 1956.
27. Sylvester, J. A.: AM. J. OBST. & GYNEC. 67: 342, 1954.
28. Wrigley, A. J.: Proc. Roy. Soc. Med. 39: 569, 1946.

MISSED LABOR WITH AUTOPSY AFTER EIGHT YEARS

MORTON S. KAUFMAN, M.D., AND DONALD WALTERS, M.D.,
WASHINGTON, D. C.

(From the Department of Obstetrics and Gynecology, Sibley Hospital)

WE FEEL it is unusual to follow a case from its inception to its termination 8 years later. This case was previously reported in the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY in January, 1952, by Kotz, Kaufman, and Hageage.[1] In that article the literature was reviewed.

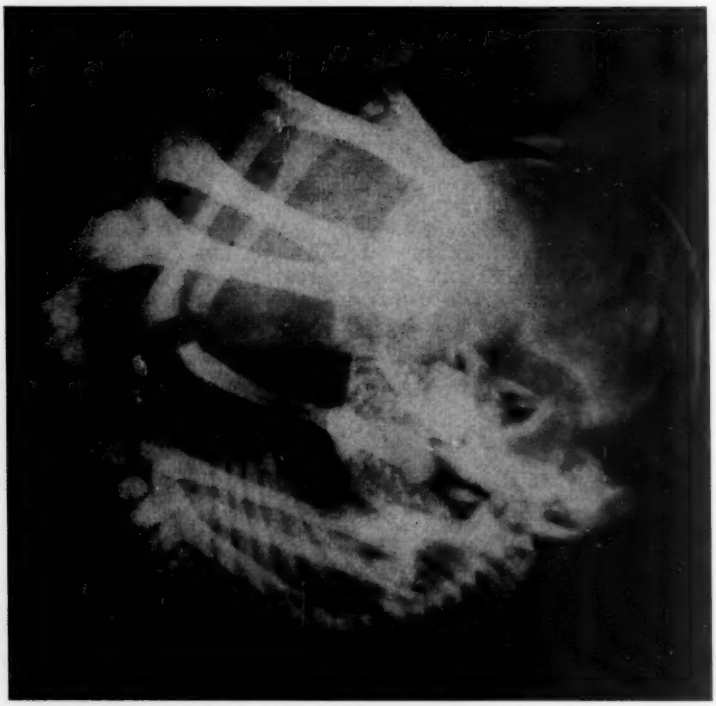

Fig. 1.—X-ray of extirpated uterus.

The patient was a 32-year-old gravida iii, para ii, with the expected date of confinement in December, 1948. The fetal movements stopped near term. X-ray evidence of fetal death was obtained and published in the previous report.

Five attempts at induction of labor were made with castor oil, enemas, Pitocin, and stilbestrol. After April, 1949, the patient refused further attempts at induction or surgical intervention. In May, 1949, she began menstruating regularly, and the uterus decreased to 2 fingerbreadths above the symphysis. X-rays taken in 1950 and 1951 were published in the previous report. After 1951, the patient refused to have further x-rays. On Nov. 23, 1956, she died of a cause not related to her pregnancy. An autopsy was performed and, through the courtesy of Dr. Norman Comeau, the entire uterus was extirpated and turned over to us. X-ray photographs of the excised uterus were made by Dr. Stecker (Fig. 1).

The specimen consisted of a uterus with attached adnexa and contained a fetus in situ (Fig. 2). The over-all dimensions were 43 by 51 cm. A considerable degree of fibrosis

could be observed in the uterine wall. The cervix showed a few old, well-healed scars, but was otherwise not unusual. The uterine canal was obliterated in the entire upper portion by the fetus. In the lower 2 cm. there appeared to be an endometrial lining into which a small amount of hemorrhage had occurred. The fetus measured approximately 42 cm. in length with no visible malformations. The fetal tissues were hard and dry and calcified in some areas. The umbilical cord was withered and the placenta barely visible. The specimen has not been disturbed except for the anterior midline opening. A section taken from an inconspicuous part of the fetus showed complete loss of all histological detail. A section of the uterine wall showed marked fibrosis. No remnants of decidua could be found.

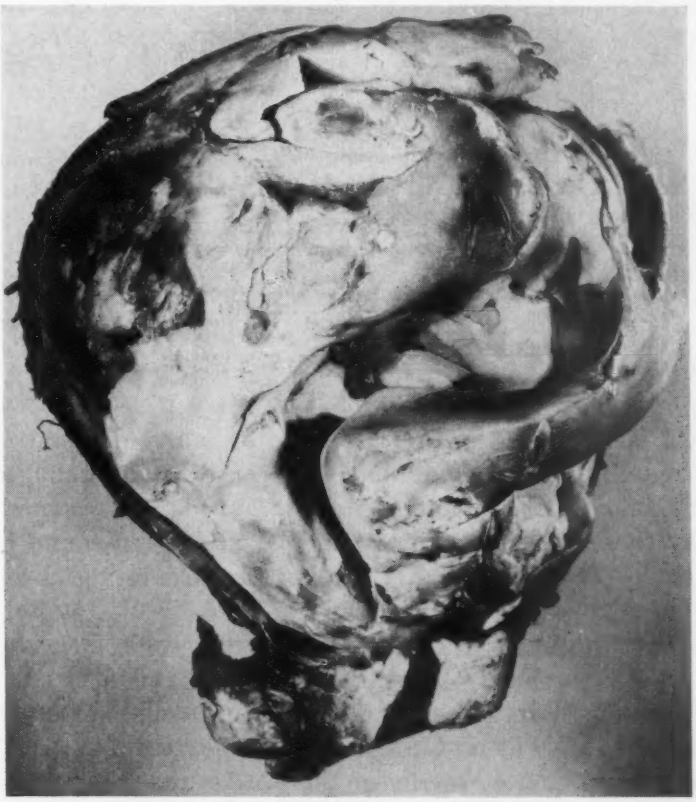

Fig. 2.—Uterus with intact fetus.

Conclusions

Several aspects of this case are noteworthy. We are unable to find any case in the literature in which missed labor has been followed from the death of fetus to the death of the mother 8 years later. One of the problems which we hoped to solve but which must remain unsolved is the length of time it takes the unexpelled fetus to become calcified. As the x-ray shows, there has been very little calcification of the soft tissues in this 8 year period. The fetus is in a remarkably good state of preservation.

The photographs and description of the specimen are through the courtesy of the Armed Forces Institute of Pathology.

Reference

1. Kotz, J., Kaufman, M. S., and Hageage, C.: Am. J. Obst. & Gynec. 63: 209, 1952.

Gynecology

CLINICAL MANIFESTATIONS OF HYPOMETABOLISM IN WOMEN

HENRY M. FOSTER, M.D., HAYS, KAN.

(From the Department of Obstetrics and Gynecology, the Eddy Clinic)

SUBNORMAL activity of the thyroid gland or faulty delivery or utilization of the circulating thyroid hormone will cause hypometabolism.[1-3] When it is caused by subnormal activity of the thyroid gland, hypometabolism may be detected by the subnormal values obtained in protein-bound iodine (PBI) and radioactive-iodine uptake (RAI) tests of the circulating hormone. When it is caused by faulty delivery or utilization of the circulating hormone, hypometabolism is more difficult to detect by objective tests since the amount of circulating hormone is usually normal. Thus, PBI and RAI test results will not reveal the metabolic insufficiency.[1, 4, 5] In both causes of hypometabolism, the basal metabolic rate will be depressed to some extent, but often the amount of depression will not be noteworthy or the test results may not be completely reliable.

Because of the difficulty, expense, and possible unreliability of laboratory tests for diagnosing hypometabolism, it is of great importance to the physician to know the clinical signs and symptoms of the disorder. In 1954, in a detailed clinical report, Watson[6] described the incidence of hypometabolism in men and women, the symptoms and physical findings, and the efficacy of therapy with desiccated thyroid. During 1955 and 1956, a survey similar to Watson's, but limited to the clinical evidence of hypometabolism in women, was carried on at the Gynecologic Service of the Eddy Clinic—a general medical clinic serving central Kansas. This report presents the findings of this survey and describes the efficacy of therapy with liothyronine (3, 5, 3′ L-triiodothyronine).

Liothyronine, the physiologically active isomer of triiodothyronine, produces all of the qualitative metabolic and clinical effects of desiccated thyroid and thyroxine but differs quantitatively in being much more rapid in action

and about three to four times as potent as an equal amount of L-thyroxine.[7] Recent studies have demonstrated that L-thyroxine is converted to liothyronine in various peripheral tissues and that liothyronine is probably the ultimate metabolically active substance.[7]

Incidence

During 1955 and 1956, approximately 800 women were treated for the first time at the Eddy Clinic. Of these new patients, 102 (approximately 13 per cent) had diagnoses by laboratory tests and clinical observation of hypometabolism. So far as could be determined, none of these 102 women had ever received thyroid therapy and none had had postoperative or previously demonstrated hypothyroidism.

In addition to the 102 patients with no histories of previous thyroid therapy, 90 hypometabolic women were found who had received therapy with desiccated thyroid without being completely relieved of their symptoms at dosages they could tolerate. The maximum doses of desiccated thyroid these patients could tolerate ranged from ½ to 10 grains daily with a median dose of 1½ grains daily. Thyroid dosages were raised beyond tolerance in all 90 of these patients in an attempt to "break through" their thyroid resistance, but none of the women responded.

The median age of the 192 women included in the evaluation was 45 years, with a range of from 17 to 70 years.

TABLE I. CHANGES IN SIGNS AND SYMPTOMS OF HYPOMETABOLISM

	PREVIOUSLY UNTREATED PATIENTS				THYROID-RESISTANT PATIENTS			
	BEFORE THERAPY		AFTER THERAPY		BEFORE THERAPY		AFTER THERAPY	
CLINICAL FINDINGS	NO.	%	NO.	%	NO.	%	NO.	%
Total no. of patients	102	100.0	53	52.0	90	100.0	51	55.6
Chronic fatigue	89	87.3	22	21.6	63	70.0	23	25.6
Enlarged thyroid gland	89	87.3	19	18.6	36	40.0	15	16.7
Dry hair	83	81.4	23	22.6	52	57.8	19	21.1
Nervousness and irritability	58	56.8	22	21.6	51	56.6	23	25.6
Dry skin	40	39.2	10	9.8	15	16.7	6	6.7
Abdominal distention	35	34.3	5	4.9	9	10.0	2	2.2
Hypersensitivity to cold	27	26.5	1	1.0	12	13.3	0	0
Dyspnea	16	15.7	1	1.0	7	7.8	0	0
Edema	11	10.8	0	0	9	10.0	0	0
Depression	9	8.8	0	0	5	5.6	1	1.1
Aches and pains	8	7.8	2	2.0	7	7.8	3	3.3
Chronic headaches	7	6.9	1	1.0	9	10.0	1	1.0
Anxiety	7	6.9	0	0	5	5.6	0	0
Anemia	3	2.9	0	0	3	3.3	0	0
Gynecologic disorders	68	66.6	5	4.9	40	44.5	8	8.9

Clinical Findings

All patients had one or more general signs and symptoms of hypometabolism. As shown in Table I, the most common findings were chronic fatigue, diffusely enlarged thyroid gland (enlargement usually slight), dry hair, gynecologic disorders, and nervousness and irritability. Somewhat less common were abdominal distention, indigestion, and constipation; hypersensitivity to cold; dyspnea; edema; depression; general aches and pains; headaches; anxiety; and anemia. The median number of findings in patients who had not received previous therapy with thyroid medications was 9 signs and

symptoms (range from 3 to 14); the median number of findings in patients with incomplete responses to desiccated thyroid was 5 signs and symptoms (range from 2 to 14).

Gynecologic Findings.—Gynecologic disturbances were recorded in 68 of the previously untreated women (66.6 per cent of the group) and in 40 of the thyroid-resistant patients (44.5 per cent of the group). Twenty-one of the previously untreated patients (20.6 per cent) and 17 of the thyroid-resistant patients (18.9) had histories of long-term infertility. All had tried unsuccessfully for 3 or more years to become pregnant or to deliver a living child.

The gynecologic disturbances appeared to be of two types: those associated generally with hypometabolism—menstrual irregularity, vaginal discharge, metrorrhagia, and dyspareunia; and those that seemed grouped together in what might be called the "pelvic congestion syndrome"—adnexal congestion, pelvic pain, adnexal tenderness, blue cervix, blue vagina, and a soft enlarged uterus.

TABLE II. CHANGES IN GYNECOLOGIC DISTURBANCES

	PREVIOUSLY UNTREATED (68 PATIENTS)				THYROID RESISTANT (40 PATIENTS)			
	GENERAL HYPOMETABOLISM		PELVIC CONGESTION		GENERAL HYPOMETABOLISM		PELVIC CONGESTION	
DISTURBANCES	BEFORE THERAPY	AFTER THERAPY	BEFORE THERAPY	AFTER THERAPY	BEFORE THERAPY	AFTER THERAPY	BEFORE THERAPY	AFTER THERAPY
All gyecologic disorders	39	2	29	3	23	6	17	2
Menstrual irregularity	17	1	12	3	10	5	5	2
Vaginal discharge	7	0	8	0	1	1	5	0
Metrorrhagia	5	0	9	0	3	0	3	0
Dyspareunia	5	0	9	0	2	0	5	0
Adnexal congestion	0	0	29	3	1	1	17	0
Pelvic pain	7	0	22	2	4	0	11	0
Adnexal tenderness	2	0	23	2	1	1	15	0
Abdominal tenderness	5	1	13	1	1	0	8	1
Blue cervix	2	0	15	2	1	0	9	0
Blue vagina	0	0	11	1	0	0	7	0
Uterus soft and enlarged	1	0	4	1	0	0	6	0
Infertility	18	4	4	0	15	3	2	1
Pregnant	–	7	–	3	–	7	–	1
Regular menses	–	7	–	1	–	5	–	0

The difference in incidence of the various gynecologic signs and symptoms is presented in Table II. Thirty-nine patients who had not previously been treated with thyroid therapy were found to have only general gynecologic disturbances. The median number of findings was 2 (range from 1 to 4). Twenty-three patients who were incompletely responsive to therapy with desiccated thyroid had only general disturbances. They had a median number of one gynecologic disturbance (range from one to 3). The disorder most frequently encountered in these patients was menstrual irregularity. Other disturbances such as vaginal discharge, metrorrhagia, or dyspareunia were noted in only a small number of patients. None of these patients suffered from adnexal congestion and few reported any pelvic pain, adnexal tenderness, or abdominal tenderness (Table II).

Twenty-nine patients who had not received previous therapy were found to have the signs and symptoms associated with the pelvic congestion syndrome. They had a median number of 5 signs and symptoms (range from 3 to 11). Seventeen patients who had not received previous therapy were

found to have the pelvic congestion syndrome. They too had a median number of 5 signs and symptoms (range from 3 to 9). All patients who suffered from the pelvic congestion syndrome had adnexal congestion, and most also had pelvic pain and adnexal tenderness. In addition, abdominal tenderness, blue cervix, or blue vagina was found in most of these patients (Table II).

Medication

Doses of liothyronine* were individualized for each patient. Therapy was begun with doses of 12.5 mcg. daily and the amount of medication was increased gradually until signs and symptoms disappeared or the maximum dose the patient could tolerate was reached. Most patients responded to 25 or 50 mcg. daily (range from 12.5 to 87.5 mcg. daily). Patients received medication for from 1 to 18 months with a median duration of therapy of 5 months.

Responses

Patient responses to liothyronine therapy were evaluated for the number and severity of the clinical signs and symptoms of hypometabolism. The severity was noted as "less severe," "same severity," and "more severe."

Almost all of the 102 patients who had not received previous thyroid therapy responded well to liothyronine medication. On the optimum doses of liothyronine 49 women (48.0 per cent of the group) were entirely relieved of all signs and symptoms of hypometabolism; another 49 women had a reduction in the number and severity of signs and symptoms; and only 4 patients (4.0 per cent) showed no important improvement under therapy. Before liothyronine therapy the average untreated patient had 9 signs and symptoms; under liothyronine therapy the average patient who had any manifestations of hypometabolism had only 2 less severe signs or symptoms.

As shown in Table I, the incidence of such general clinical findings as fatigue, enlarged thyroid, dry hair, gynecologic disorders, and dry skin were reduced to about one fourth of their pretherapy frequency. Other signs and symptoms were reduced even more and some, such as edema, depression, anxiety, and anemia, were eliminated entirely.

Equally good responses to liothyronine therapy were seen in the 90 women who had unsatisfactory responses to desiccated thyroid. Thirty-nine patients (43.4 per cent of the group) were completely freed of all clinical signs and symptoms of hypometabolism; 43 patients (47.7 per cent) had a reduction in the number and severity of signs and symptoms; 6 patients (6.7 per cent) showed no important improvements under therapy; and 2 patients (2.2 per cent) said they felt worse. While on desiccated thyroid therapy the average patient had 5 signs and symptoms of hypometabolism; under liothyronine therapy, the average patient who had any manifestations of the disorder had only 2 less severe signs or symptoms.

It is interesting to note in Table I that although before therapy there were differences in the incidences of the various signs and symptoms in the patients who had not received previous medication and those who were intolerant to desiccated thyroid, after liothyronine therapy the incidence of signs and symptoms was almost identical. For example, before liothyronine therapy the incidence of dry hair in previously untreated patients was 81.4 per cent and in thyroid-resistant patients was 57.8 per cent; after liothyronine therapy the incidence was 22.6 per cent and 21.1 per cent, respectively.

*Cytomel, Smith Kline & French Laboratories, Philadelphia, Pa.

Gynecologic Findings.—As shown in Tables I and II, women with general gynecologic disorders responded well to therapy. Of 39 women who had not previously been treated with thyroid therapy, 37 were completely relieved of all gynecologic signs and symptoms under liothyronine therapy. Similar good responses were observed in the 23 women who had not responded to thyroid therapy. Under liothyronine therapy, 17 of these women were completely relieved of all signs and symptoms.

Patients with signs and symptoms of the pelvic congestion syndrome also responded extremely well to liothyronine therapy. Of 29 previously untreated women, 26 were completely relieved of all signs and symptoms; of 17 thyroid-resistant women, 15 were completely relieved of all signs and symptoms.

Patients who suffered from long-term infertility responded very well to liothyronine therapy. Of 22 infertile women who had not received previous thyroid therapy, 10 became pregnant. Eight who had suffered from amenorrhea began to menstruate regularly, and only 4 showed no improvement. Of 17 infertile women who had not responded to thyroid therapy, 8 became pregnant on liothyronine and 5 others who had not menstruated before liothyronine therapy began to menstruate regularly. Four patients showed no improvement on liothyronine therapy (Table II).

Case Histories

The following case histories are typical of those of patients who received liothyronine therapy:

Patient 14779 was a dull, apathetic woman of 30. She suffered from severe chronic fatigue, was nervous and irritable, and had a severe hypersensitivity to cold. Her menses were irregular and she suffered from severe abdominal distention and constipation. Her hair and skin were dry and coarse and the thyroid gland was slightly enlarged. She weighed 172 pounds (about 25 pounds overweight) and was unable to remain on a diet.

The patient was started on liothyronine therapy, 12.5 mcg. daily, and the dosage was raised gradually until at 75 mcg. daily her signs and symptoms of hypometabolism began to disappear. Within 2 months at this dosage she was completely free of all signs and symptoms and her weight had fallen to 148 pounds. She had become bright, interesting, and alert. After almost a year of therapy on a maintenance dose of 75 mcg. of liothyronine daily, she has had no recurrence of any of the signs and symptoms of hypometabolism.

Patient 18862 was typical of the women with long-term infertility and the pelvic congestion syndrome who were benefited by liothyronine therapy. When first seen she had amenorrhea, dyspareunia, a soft enlarged uterus, adnexal congestion, and severe pelvic pain which developed after she got out of bed and which persisted and increased in intensity as long as she was on her feet. She had tried for 6 years to become pregnant, but without success. In addition, she had 14 signs and symptoms of hypometabolism including chronic fatigue, listlessness, nervousness and irritability, chronic hypersensitivity to cold, abdominal distention and constipation, dyspnea, moderate depression, and dry skin and hair.

Liothyronine therapy was begun at 12.5 mcg. daily and on this dosage all of her signs and symptoms of hypometabolism either disappeared or were reduced in severity. After a month of therapy, she menstruated, and after the second month of therapy she became pregnant. She is now in the eighth month of a normal pregnancy and is being maintained on 12.5 mcg. of liothyronine daily.

The difference in response to desiccated thyroid and liothyronine was often quite pronounced.

Patient 15543 was a 20-year-old girl who suffered from severe hypometabolism. The most outstanding signs and symptoms were a severe listlessness, depression, nervousness,

and irritability. She was chronically fatigued, hypersensitive to cold, and gained weight easily. Her skin and hair were dry and coarse. Although she was intelligent, she had failed at college because she could not apply herself to her studies.

A daily dose of 1½ grains of desiccated thyroid, the maximum amount she could tolerate without side effects, eliminated many of her complaints, but she remained severely depressed and moderately fatigued and nervous. Her hair continued to be dry, and she continued to gain weight. The dosage of thyroid was increased to 3 grains daily in an effort to "break through," but without success. The patient remained fat, slatternly, fatigued, and depressed.

Liothyronine therapy was begun at 12.5 mcg. daily. After a week, the dosage was raised to 25 mcg. daily. At this dosage, her fatigue, nervousness, and irritability disappeared. Her skin and hair became normal; she stopped gaining weight, and in a few weeks she lost 17 pounds. Now, after 9 months on a daily maintenance dose of 25 mcg. of liothyronine, she is a neat, attractive, lively young girl. She has been readmitted to college and is doing well in her studies and she has dates regularly.

The case history of Patient 9792 is typical of the patients who had what may be called the pelvic congestion syndrome along with clinical manifestations of hypometabolism.

This 21-year-old woman had suffered from apparent hypometabolism since puberty. The clinical findings included chronic and severe fatigue, nervousness and irritability, headaches, general aches and pains, depression, anxiety, hypersensitivity to cold, abdominal distention, constipation, and indigestion. She also suffered from premenstrual tension, pelvic pain, and dyspareunia. The menses, however, were normal. The abdomen was tender and she had a blue vagina and cervix, a soft and enlarged uterus, and adnexal congestion and tenderness.

Therapy was begun with desiccated thyroid, but doses up to 2.5 grains daily, the maximum she could tolerate without side effects, were of no benefit. None of the signs or symptoms was reduced in severity. The dosage of desiccated thyroid was raised to 3.5 grains daily in an attempt to "break through" her intolerance, but to no avail.

Liothyronine therapy was instituted at 12.5 mcg. daily and raised to 37.5 mcg. daily in a 2 week period. On 37.5 mcg. of liothyronine each day, all of the patients' signs and symptoms of hypometabolism disappeared. Moreover, the tender abdomen, blue cervix and vagina, and other signs suggesting pelvic congestion also disappeared. The patient has been maintained for the past year on 37.5 mcg. of liothyronine daily, with no recurrences of her disorders.

Comment

The incidence of hypometabolism of approximately 13 per cent observed at the Eddy Clinic is approximately 10 times the incidences of 1.2 and 1.3 per cent reported in the literature,[6, 8] and may reflect a higher incidence in this locality; however, the incidence of the various signs and symptoms of hypometabolism differs somewhat from that reported by others. Watson,[6] for example, noted cold intolerance in 59.4 per cent of the patients he observed; in this evaluation, hypersensitivity to cold was noted in only 26.5 per cent of the patients who had not received previous thyroid therapy. On the other hand, dry hair noted in 81.4 per cent of the untreated patients in this evaluation is not mentioned among Watson's clinical findings. On the whole, however, the types of clinical findings do agree, and differences in their incidence are probably due to the different scopes of the evaluations and to differences in emphasis by the investigators.

Duncan and Taylor[9] described the pelvic congestion syndrome as being characterized by lower abdominal pain and parametrial tenderness without apparent cause. Taylor[10] and Kroger and Freed[11] suggested that the disorder may be psychosomatic in origin, but the good responses observed under liothyronine therapy indicate that in some patients at least the pelvic congestion syndrome may be due to definite endocrine imbalance.

For other gynecologic disorders, the use of a thyroid preparation needs no explanation. As Ferrer and McGavack[12] pointed out, there is "a more than coincidental relationship between thyroid disease and pelvic disorders," and "even though sharply defined manifestations of diminished thyroid function are absent,"[13] a therapeutic test with thyroid is justified. The major point of interest in this evaluation was that many patients who were incompletely relieved by desiccated thyroid therapy were completely relieved by liothyronine. Other investigators[3, 4] have similarly noted that most patients with gynecologic disturbances and infertility respond better to liothyronine than to other thyroid preparations.

Although the stress of this report is on the clinical signs and symptoms of hypometabolism, the importance of laboratory tests must not be ignored. Determinations of the basal metabolic rate (BMR), protein-bound iodine (PBI), radioactive-iodine uptake (RAI), serum cholesterol, and other tests should be taken into consideration when it is possible or practical to perform them. Practically, however, it must be recognized that few institutions are capable of or willing to carry out these tests, and one certainly should not defer a tentative diagnosis and therapeutic trial with liothyronine in patients suspected of hypometabolism.

Summary

Hypometabolism, whether caused by a subnormal activity of the thyroid gland or faulty delivery or utilization of thyroid products, was found to occur in 13 per cent of the approximately 800 women treated at the gynecologic service of a general clinic during 1955 and 1956.

The most common signs and symptoms of hypometabolism were chronic fatigue, enlarged thyroid gland, gynecologic disorders, dry hair, and nervousness and irritability. The most frequent gynecologic disorders were adnexal congestion, pelvic pain, adnexal tenderness, and menstrual irregularity.

Liothyronine (3, 5, 3′ L-triiodothyronine) proved to be an effective medication for relieving the clinical signs and symptoms of hypometabolism.

Of 102 women who had never received thyroid medication prior to treatment with liothyronine, 49 women (48.0 per cent of the group) were entirely relieved of all signs and symptoms by liothyronine and another 49 women (48.0 per cent) had a reduction in the number and severity of signs and symptoms. Only 4 women (4.0 per cent) showed no improvement under liothyronine therapy. Before therapy, the median number of signs and symptoms in these patients was 9; under therapy, the average patient who had any manifestations of hypometabolism had only 2 and these were less severe.

Of 90 women who were incompletely responsive to therapy with desiccated thyroid in doses that they could tolerate, 39 women (43.4 per cent of the group) were completely freed of all clinical signs and symptoms of hypometabolism when they received liothyronine therapy. Forty-three patients (47.7 per cent) had a reduction in the number and severity of signs and symptoms when receiving liothyronine therapy; 6 patients (6.7 per cent) showed no important improvement; and 2 patients (2.2 per cent) said they felt worse. While on desiccated thyroid therapy the average patient had 5 signs and symptoms of hypometabolism; under liothyronine therapy, the average patient who had any manifestations of the disorder had only 2 less severe signs or symptoms.

Although the stress of the report is on the clinical signs and symptoms of hypometabolism, the importance of laboratory tests must not be ignored. In the absence of laboratory tests, however, a therapeutic trial with liothyronine in patients suspected of hypometabolism is often desirable and beneficial. Since many patients who are incompletely responsive to thyroid hormone respond to liothyronine, the latter is the preferable drug for trial.

References

1. Kurland, G. S., Hamolsky, M. W., and Freedberg, A. S.: J. Clin. Endocrinol. **15**: 1354, 1955.
2. Kurland, G. S., Bustos, J. G., Hamolsky, M. W., and Freedberg, A. S.: J. Clin. Endocrinol. **17**: 1365, 1957.
3. Morton, J. H.: J. A. M. A. **165**: 124, 1957.
4. Kupperman, H. S.: S. Clin. North America **37**: 517, 1957.
5. Gold, A.: Canad. Services M. J. **12**: 619, 1956.
6. Watson, B. A.: New York J. Med. **54**: 2045, 1954.
7. Council on Drugs: Sodium Liothyronine, J. A. M. A. **164**: 972, 1957.
8. Christman, H. E.: Ohio M. J. **46**: 965, 1950.
9. Duncan, C. H., and Taylor, H. C., Jr.: Am. J. Obst. & Gynec. **64**: 1, 1952.
10. Taylor, H. C., Jr.: Am. J. Obst. & Gynec. **57**: 637, 1949.
11. Kroger, W. S., and Freed, S. C.: Psychosomatic Gynecology, Philadelphia, 1951, W. B. Saunders Company, pp. 423-430.
12. Ferrer, F. P., and McGavack, T. H.: Am. J. Surg. **85**: 67, 1953.
13. McGavack, T. H.: The Thyroid, St. Louis, 1951, The C. V. Mosby Company.

EFFECT OF PREDNISONE* ON ABNORMAL MENSTRUAL FUNCTION

WILLIAM H. PERLOFF, M.D., AND BERTRAM J. CHANNICK, M.D.,
PHILADELPHIA, PA.

(From the Department of Endocrinology and the Department of Medicine, Temple University School of Medicine and Medical Center)

PREDNISONE reduces or eliminates excess hair growth in women with "idiopathic hirsutism"[1] or, a preferable term, "adrenal virilism."[2] While studying this phenomenon, we noted concurrent improvement in the menstrual status of patients with amenorrhea, menometrorrhagia, anovulation, and infertility. Intrigued by this desirable development, we treated women with menstrual abnormalities, with and without hirsutism, by this means, and the purpose of this paper is to report our observations.

Material and Methods

Forty-three patients comprise the subject of this report as follows:

Proved Stein-Leventhal syndrome (polycystic ovaries)	12
Presumed Stein-Leventhal syndrome	14
Follicular cysts of ovaries	7
Anovulatory bleeding	7
Pituitary amenorrhea	3
Total	43

Following a complete medical and gynecological history and physical examination, these tests were performed: complete blood count, routine urinalysis, sedimentation rate, protein-bound iodine, cholesterol, glucose tolerance, urinary estrogens, gonadotropins, 17-ketosteroids and corticoids, serial cervical mucus inspection, basal body temperature record, and, when possible, endometrial biopsies. In this way, pituitary-ovarian function was evaluated, and the possibility was excluded of other endocrine abnormalities such as Cushing's syndrome or other androgenic entities.

Prednisone was administered in daily doses of 10 mg. for 4 weeks, then 5 mg., and, in some cases, 2.5 mg. for the total number of days indicated in Table I. In certain instances, 10 mg. was given for 5 consecutive days starting on the fifth to the seventh day of the menstrual cycle.

Results

Eleven of the 45 women obtained little or no improvement, because of irregular or inadequate therapy, or reasons not clear to us. Table I lists only

*The liberal supply of prednisone (Meticorten) furnished by the Schering Corporation is gratefully acknowledged.

the patients who derived benefit from treatment. Of the 9 individuals with proved polycystic ovaries (Stein-Leventhal syndrome), 6 showed major and 2 showed minor degrees of hirsutism; 3 were obese; and 8 had grossly irregular menses or amenorrhea. Only one complained of infertility; others did not desire conception. Prednisone therapy for 160 to 360 days resulted in complete or satisfactory regulation of menstrual function, including conception in the patient previously infertile. Significant improvement was not noted in most instances for 3 months and maximum benefit occurred by 6 months. Hirsutism diminished in all patients; this will be the subject of another report.[2]

Eleven patients had clinical and laboratory stigmas of adrenal virilism with associated Stein-Leventhal syndrome; the ovarian diagnosis was not confirmed surgically. Three were obese, all were hirsute and menstruated in a grossly irregular fashion, and 3 complained of infertility. Treatment continued for up to 420 days as indicated in Table I and improved menstrual function and/or fertility were achieved in all.

The next group consists of 6 women with menstrual dysfunction associated with follicular cysts of the ovaries as indicated either by abdominal exploration or by endometrial biopsy. D. W. received 10 mg. of prednisone a day for 5 consecutive days starting with the seventh day of the cycle. After the first month, a normal ovulatory menstrual flow occurred, and during the next month she conceived, whereas E. T., despite 5 such courses of therapy and consequent regular ovulatory menses, did not. N. K., infertile for 2 years, took 5 mg. daily for 35 days, and conceived without a subsequent menstrual flow. D. H. was treated with 10 mg. a day for 30 days and 5 mg. a day for an additional 180 days with the onset of periodic menses, which persisted to the time of writing, despite elimination of therapy. Menstrual regularity was maintained in M. H. with 5 mg. a day for a total of 5 months. E. S. had one normal flow after 30 days of hormone treatment and conceived the following month with no medication.

The diagnosis of anovulatory bleeding was made only after 6 or more months of personal observation, and depended upon monophasic basal body temperature graphs, faulty cervical mucus changes, and absence of secretory endometrium. Four of 7 patients conceived, although one, A. S., miscarried at 6 weeks. Two of 3 women with pituitary amenorrhea began to menstruate regularly, and one has continued to do so to date, 3 months after cessation of therapy. Subjective and objective improvement in one patient with fibroadenosis, and another with chronic cystic mastitis was noted as indicated in Table I.

Comment

Jones and associates[3] reported improvement in the menstrual status of similar patients from cortisone, an observation confirmed by others.[4, 5] On the basis of his experience with such problems, Greenblatt[4] has postulated 3 types of patients, those with maximal improvement from ovarian wedge resection, those who respond most to cortisone therapy, and those who react best to a combination of both modalities of treatment. Whether one can, in fact, group patients in this way is not clear, but the desirability of first attempting medical management is illustrated by identical twins, Jane and June B., who were amenorrheic. Jane was subjected to abdominal exploration when polycystic (Stein-Leventhal) ovaries were found, and wedge resection of the ovaries was performed. Several menstrual periods at irregular intervals followed, after which amenorrhea recurred. Both sisters were given prednisone, and regular or almost regular rhythm developed within 6 months, and continued to the present. We believe that women with the Stein-Leventhal

TABLE I. EFFECT OF PREDNISONE ON ABNORMAL MENSTRUAL FUNCTION

PATIENT	AGE	OBESITY	HIRSUTISM	MENSTRUAL STATUS	INFERTILITY (YEARS)	PREDNISONE DOSE	PREDNISONE DAYS	MENSTRUAL STATUS	CONCEPTION
Stein-Leventhal Syndrome.—									
B. W.	24	2	4	Grossly irreg.	-	10-5	180	Improved	-
U. B.	30	0	4	Grossly irreg.	-	10-5	360	Improved	-
E. V.	26	2	4	Regular anovul.	6	10-5	160	Improved	+
A. P.	30	2	4	Amenorrhea	-	10-5	167	Improved	-
D. S.	26	0	3	Grossly irreg.	-	10-5	360	Improved	-
R. B.	21	0	3	Grossly irreg.	-	10-5	265	Improved	-
Ja. B.	16	0	2	Amenorrhea	-	10-5	180	Improved	-
Ju. B.	16	0	2	Amenorrhea	-	10-5	180	Improved	-
P. N.	20	0	0	Amenorrhea	-	10-5	280	Improved	-
Stein-Leventhal Syndrome Presumed.—									
V. C.	42	1	3	Grossly irreg.	-	10-5	234	Improved	-
S. P.	25	0	3	Grossly irreg.	-	10-5	268	Improved	-
S. S.	23	0	3	Grossly irreg.	-	10-5	357	Improved	-
M. G.	27	0	3	Grossly irreg.	-	10-5	234	Improved	-
R. V.	28	2	2	Grossly irreg.	4	10-5	236	Improved	+
E. B.	31	0	2	Grossly irreg.	-	10-5	406	Improved	-
E. D.	20	0	2	Grossly irreg.	-	10-5	420	Improved	-
R. C.	31	2	2	Grossly irreg.	-	10-5	370	Improved	-
D. R.	25	0	2	Grossly irreg.	5	10-5	270	Improved	+
J. P.	18	0	2	Grossly irreg.	-	10-5	268	Improved	-
J. A.	22	0	1	Grossly irreg.	3	5	60	Improved	
						0	60	Amenorrhea	
						2.5	30		+
Follicular Cysts.—									
D. W.	27	0	0	Grossly irreg.	4	10	5×2	Improved	+
E. T.	24	1	0	Grossly irreg.	3	10	5×5	Improved	0
N. K.	23	0	0	Grossly irreg.	2	10	35		+
D. H.	21	2	0	Grossly irreg.	-	10	30	Amenorrhea	
						5	180	Improved	
						0	90	Improved	-
M. H.	21	0	0	Grossly irreg.	-	10	30	Improved	-
						5	120	Improved	
E. S.	24	0	0	Grossly irreg.	3	5	30	Improved	
						0			+

Anovulation.—									
S. T.	27	0	0	Irregular	2	10	14		
						5	60	Improved	+
J. G.	30	0	0	Regular	7	5	40		+
D. O.	29	0	0	Regular	2½	10	5×3	Improved	
						0	30		+
A. S.	33	0	0	Regular	15	10	5	Ovulation	
						5	30	Ovulation	+
									Miscarried
Pituitary Amenorrhea.—									
E. L.	19	0	0	Amenorrhea	–	10	10		
						5	60	Improved	–
C. B.	17	0	0	Amenorrhea	–	5	60	Improved	–
						2.5	60	Improved	–
						0	90	Improved	–
Fibroadenosis by X-ray.—									
E. Y.	39	+	0	Regular	–	10	44	Breasts improved	
						5	28	Breasts improved	
						2.5	16	Breasts worse	
						5	30	Breasts improved	
Cystic Mastitis.—									
M. B.	24	0	0	Regular	–	5	180	Breasts improved	
						0	90	Breasts improved	

syndrome should be treated with 10 mg. of prednisone a day for 30 days, then 5 mg. a day for a minimum of an additional 150 days, before ovarian surgery is considered.

In an earlier communication,[6] we suggested that the Stein-Leventhal syndrome represents an ovarian manifestation of adrenal hypercorticism, involving the androgen-producing elements, such as that seen in adrenal virilism, and caused by an inherent adrenal enzymic defect which interferes with hydrocortisone synthesis. Consequent release of greater than normal amounts of pituitary ACTH results in adrenocortical hyperplasia, a course of events described by Bongiovanni.[7] If this concept is valid, the beneficial effect of prednisone, which suppresses ACTH production, is understandable. The mechanism by which prednisone improves menstrual function in women with follicular cysts of the ovaries is even less apparent. If this anomaly results from pituitary gonadotropic hormone imbalance as suggested by Greenblatt,[4] one must assume reorganization of gonadotropic hormone production and/or release by prednisone, a fascinating but unproved hypothesis. Interesting, in this connection, is the observation of Sohval and Soffer[8] that cortisone increases urinary FSH, a fact noted repeatedly by us in patients taking prednisone. One cannot help but wonder whether this action relates to the induction of ovulation in previously anovulatory women.

Prednisone caused augmentation of menopausal symptoms in some women and necessitated an increase in the maintenance dose of estrogen in others, suggesting an antiestrogen effect. Whether or not the improvement in breast discomfort noted in patients E. Y. and M. B. is on this basis, is pure conjecture.

Despite the lack of understanding concerning the mechanism of action, it is perfectly clear that cortisone constitutes an important advance in the treatment of certain gynecological disorders. Prednisone in recommended doses is equally effective, and is to be preferred because of the lower incidence of undesirable side effects. Jefferies and associates[5] suggested that intermittent treatment and varying doses of cortisone contributed to their good results. We believe that both their data and ours are insufficient to draw such conclusions, and, at the moment, generally prescribe 10 mg. of prednisone a day for 30 days and 5 mg. a day thereafter. Some patients respond quickly, whereas 6 months of treatment is required in others. The optimal duration of therapy is not yet certain. We customarily prescribe medication for approximately 2 to 3 months after regularity has been achieved and reinstitute prednisone if and when relapse occurs.

Conclusions

On the basis of this small group of patients, and recognizing that careful and long-term observation in many more is required, we suggest that prednisone therapy may be of value in the following gynecological conditions:

1. Menstrual disorders associated with the Stein-Leventhal syndrome.

2. Menstrual dysfunction from unopposed estrogen incident to follicular cysts of the ovaries and/or anovulation.

3. Infertility with regular menstrual rhythm due to hypogonadotropic anovulation.

References

1. Perloff, W. H., Hadd, H. E., Channick, B. J., and Nodine, J. H.: A. M. A. Arch. Int. Med. 100: 981, 1957.

2. Perloff, W. H., Channick, B. J., Suplick, B., and Carrington, E. R.: J. A. M. A. 167: 17, 1958.
3. Jones, G. E. S., Howard, J. E., and Langford, H.: Fertil. & Steril. 4: 49, 1953.
4. Greenblatt, R. B.: Am. J. Obst. & Gynec. 66: 700, 1953.
5. Jefferies, W. McK., Weir, W. C., Weir, D. R., and Prouty, R. L.: Fertil. & Steril. 9: 145, 1958.
6. Perloff, W. H., Channick, B. J., Hadd, H. E., and Nodine, J. H.: Fertil. & Steril. 9: 3, 1958.
7. Bongiovanni, A. M., and Eberlein, W. R.: Pediatrics 16: 628, 1955.
8. Sohval, A. R., and Soffer, L. J.: J. Clin. Endocrinol. 11: 677, 1951.

3521 North Broad Street
Philadelphia 40, Pennsylvania

NONSPECIFIC VAGINAL INFECTIONS*

A Critical Evaluation of Hemophilus Vaginalis

ANDRE HELTAI, M.D., AND PARVIZ TALEGHANY, M.D., BROOKLYN, N. Y.

(From the Department of Obstetrics and Gynecology, Methodist Hospital of Brooklyn)

THE theory that nonspecific vaginitis is caused by *Hemophilus vaginalis* has produced some controversy in the recent medical literature. This microorganism was first described by Leopold[1] in 1953, who isolated it from the urine of male patients and the cervices of women. In 1955 Gardner and Dukes[2] stated that "the vast majority of so-called 'nonspecific' bacterial vaginitides constitute a specific infectious entity caused by a single etiological agent." Others[4, 5] have tried to substantiate the findings of these workers with varying degrees of success. Some investigators[2, 3] have tried to describe and classify this organism; others[6] deny its existence as a single entity and doubt its assumed pathogenic role. This controversy continues and it appears that an agreement has not yet been reached on this matter.

The purpose of this study was to evaluate the role, if any, of this small gram-negative anaerobic microorganism as the cause of nonspecific vaginitis. The laboratory methods employed by us in this study duplicated those employed by Gardner and Dukes in detecting the presence or absence of *Hemophilus vaginalis*. We have also tried to determine from the data obtained, whether *H. vaginalis* when found was the only microorganism responsible for the signs and symptoms of this condition.

The success obtained by other workers in the treatment of so-called nonspecific vaginitis with the use of three sulfonamides in a cream form† as therapy prompted us to evaluate a new form of triple sulfonamide vaginal therapy while carrying out this study.

Materials and Methods

One hundred and twenty-seven patients were selected for this study from the Out-patient Department of the Methodist Hospital in Brooklyn, New York. This group was composed of patients from the antepartum and postpartum clinics as well as from the gynecological clinic.

These 127 cases were selected from among patients who complained of vaginal discharge, pruritus, and burning. These patients were subjected to complete pelvic examination to rule out any pathological condition of the

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†Triple Sulfa Cream, Ortho Pharmaceutical Corporation, Raritan, N. J.

uterine corpus or adnexa. All had one or more of the following signs: vaginal discharge, erosion of the cervix, endocervicitis, or evidence of vaginitis and pruritus.

The diagnosis of vaginal infection was dependent upon clinical and microbiological examination. Only those 127 patients were selected for this study in whom the presence of *Trichomonas vaginalis* was ruled out by wet mount. The material for bacteriological examination was obtained by taking a smear from the posterior fornix for Gram staining. Two separate swabs were used to collect material from the posterior fornix for culturing and were placed in a sterile glass test tube. This material was then forwarded to the hospital laboratory, where it was processed within a period of 2 hours. Specimens were then transferred from these tubes to Brewer's thioglycolate broth without indicator. Two blood agar plates were properly streaked; one was placed within a carbon dioxide candle jar, and the other was incubated aerobically. All cultures were incubated at 37° C. for 48 hours. Secretions from the lateral vaginal wall or specimens of suspicious areas if present were obtained on another applicator, which was streaked on a vial of Nickerson's medium to rule out the presence of the genus Candida.

Smears from the material obtained were examined for bacterial flora by Gram's stain before and after culturing. Small gram-negative anaerobic bacilli not found in routine aerobic cultures were considered to be *H. vaginalis* as they fulfilled the criteria described by Gardner and Dukes. Staphylococci were classified according to the pigment formation on the nutrient agar. Streptococci were classified according to their reaction on blood agar or their growth in Brewer's medium. The aerobic bacilli were streaked on Endo's medium for preliminary identification and were processed further if necessary.

When the diagnostic specimen for microbiological examination had been obtained, all patients selected for this study were given 20 vaginal tablets each. Each tablet contained sulfathiazole, sulfacetamide and N'benzoylsulfanilamide.* Patients were instructed to insert one vaginal tablet every morning and evening for a 10 day period, the medication to be continued regardless of the menstrual period. Vaginal douches were not allowed during the course of treatment. The patients were given an appointment for a follow-up visit 14 days after the beginning of treatment, that is, 4 days after the insertion of the last vaginal tablet. On this return visit the patients were questioned about their symptoms and their reactions concerning the vaginal tablets. A smear for Gram staining and a specimen for culture was obtained by the same procedure as at the first examination. This material was processed in a similar manner in the laboratory. A complete pelvic examination was performed and the appearance of the vagina and the cervix was observed and recorded.

Results

Of 127 patients, 90 returned for the second visit. The remaining 37 were not considered in the evaluation of the vaginal tablet.

A variety of microorganisms was found to be present in the vaginal flora of all 127 patients. A total of 218 cultures revealed the presence of one or more of the following bacteria:

Staphylococcus albus
Staphylococcus aureus
Streptococci (anaerobic)
Nonhemolytic streptococcus
Alpha and beta hemolytic streptococcus
Diphtheroids
Escherichia coli
Proteus vulgaris
Pseudomonas aeruginosa

*Triple sulfonamide vaginal tablets for this study were supplied by the Ortho Research Foundation, Raritan, N. J.

A small gram-negative bacillus was found in 30 cultures and always in conjunction with one or more of the other microorganisms. This organism conformed to the description of *Hemophilus vaginalis* as reported by Gardner and Dukes, and it was isolated with the use of the carbon dioxide candle jar technique. In not one instance was this so-called *H. vaginalis* the only organism present in the vagina, and consequently it was not isolated as a pure culture. The genus Candida was present in 31 cultures and was always found to be in association with some other microorganism.

The response to the therapy of vaginal tablets of the 90 patients who returned for the follow-up visit is summarized in Table I. These results were obtained following one 10 day course of triple sulfonamide in the form of a vaginal tablet.

TABLE I. SYMPTOMATIC RESULTS OF TREATMENT

RESULTS	NO. OF CASES	%
Discharge and symptoms cleared completely	44	48.8
Discharge and symptoms considerably improved	28	31.2
Total	72	80.0
No change	18	20.0

Cervical erosion was present in 22 of the 90 cases. The response to therapy is summarized in Table II.

TABLE II. EFFECT OF TREATMENT ON EROSION

RESULTS	NO. OF CASES	%
Cervical erosion cleared	14	63.6
Cervical erosion considerably improved	2	9.1
Total	16	72.7
Cervical erosion persisted	6	27.3

In 2 cases cervical erosion appeared after treatment.

Statistical Analysis

1. Classification of patients according to the incidence of *H. vaginalis* before and after treatment and clinical response to therapy is shown in Table III. In this table Group 1 represents patients in whom *H. vaginalis* was present before and after treatment. Group 2 represents patients in whom *H. vaginalis* was found before treatment but none could be demonstrated after treatment. Patients in Group 3 had no *H. vaginalis* before treatment but the organism was present after treatment. All the patients in whom no *H. vaginalis* could be demonstrated either before or after treatment are classified in Group 4.

TABLE III. RESULTS OF TREATMENT IN RELATION TO PRESENCE OF HEMOPHILUS VAGINALIS

	GROUP 1	GROUP 2	GROUP 3	GROUP 4	TOTAL
Improved	4	11	8	49	72
Not improved	1	2	4	11	18
Total	5	13	12	60	90

Application of the chi-square test of significance shows that the above classification of the *H. vaginalis* variable versus improvement is independent. In other words, there is no relationship between patient improvement (or lack of improvement) and the presence or absence of *H. vaginalis*.

2. The largest difference in proportion is observed in Group 3.

The equation $P_1 = \frac{8}{72} = .11$ shows the proportion of improved patients who did not have *H. vaginalis* before treatment but did have it after treatment.

$P_2 = \frac{4}{18} = .22$ shows the proportion of unimproved patients in same category.

The difference in these two proportions is not significant, as calculated by the t-test computation.

3. The presence or absence of certain types of microorganisms before and after treatment in patients with mild, moderate, or heavy discharge seemed to occur in a random fashion. No differences could be detected when certain types of germs were present or absent in the improved and unimproved groups.

Comment

The results of this study indicate that a variety of microorganisms must be considered in nonspecific vaginitis, since they were found in vaginal cultures both before and after treatment. The mere presence of a microorganism in the vaginal flora does not necessarily mean that it is the etiological agent of vaginitis, discharge, or cervical erosion. This point is well illustrated by some cases in which we obtained a satisfactory response to therapy, as related to symptoms and clinical findings, but where cultures consistently showed the presence of one or more microorganisms.

The so-called *Hemophilus vaginalis* was never present as a single entity, but was always associated with some other microorganism. In 3 instances it was present before and after treatment, although these patients were asymptomatic following therapy. It was found to be present following treatment in 12 cases, where it was not demonstrated previously. In 8 of these cases the patient's nonspecific vaginitis had responded to therapy both symptomatically and clinically.

The presence of these bacteria in the vagina does not appear to be any more significant than the presence of the numerous other organisms observed in nonspecific vaginitis. Certainly, our data do not substantiate their role as an etiological agent causing this disease.

The response to therapy had nothing to do with the presence of a specific organism, multiplicity of any one microorganism, or with patterns of grouping. We feel, therefore, that in nonspecific vaginitis there is no need to make cultures from the vaginal flora in an attempt to identify the microorganism believed to be responsible for the clinical symptoms.

The satisfactory results obtained with the new vaginal tablet containing three sulfonamides: sulfathiazole, sulfacetamide, and N′benzoylsulfanilamide suggest that it would be a useful addition to our gynecological armamentarium. These tablets were readily accepted by all the patients; they are easy to use and dissolve rapidly. The clinical response obtained with the new vaginal tablet is comparable to that obtained with the same three sulfonamides in cream form. The vaginal discharge was rapidly controlled and the cervical erosions were cured in a high percentage of patients.

Summary

1. The results of this investigation clearly demonstrate the presence of a gram-negative bacillus conforming to the description of *Hemophilus vaginalis* in the vaginal flora.

2. This organism was never isolated in pure culture, but was always found to be associated with one or more bacteria.

3. No evidence was found that suggested *H. vaginalis* to be the etiological agent in nonspecific vaginitis.

4. A new form of triple sulfonamide therapy, a vaginal tablet, was found to be equally as effective and acceptable as triple sulfonamide therapy in the form of a cream.

We express our thanks to Miss Phoebe H. Walker, M.S., bacteriologist at the Methodist Hospital of Brooklyn, for the bacteriological examinations, as well as to Dr. Luis F. Nanni, associate professor, Rutgers University, for the statistical analysis.

References

1. Leopold, S.: U. S. Armed Forces M. J. 4: 263, 1953.
2. Gardner, H. L., and Dukes, C. D.: Am. J. Obst. & Gynec. 69: 962, 1955.
3. Deming, J. E.: Northwest Med. 54: 992, 1955.
4. Ray, J. L., and Maughan, G. M.: West. J. Surg. 64: 581, 1956.
5. Gardner, H. L., Dampeer, T. K., and Dukes, C. D.: Am. J. Obst. & Gynec. 73: 5, 1080, 1957.
6. Brewer, J. I., Halpern, B., and Thomas, G.: Am. J. Obst. & Gynec. 74: 834, 1957.

COMPARISON OF BATTERY pH READINGS AND ELECTRONIC pH RECORDINGS OF THE VAGINA IN TRICHOMONAS VAGINALIS INFESTATION

A Report of 255 Consecutive Readings Over a Period of 143 Days in One Patient

KARL JOHN KARNAKY, M.D., HOUSTON, TEXAS

(From the Obstetrical and Gynecological Research Institute)

TRICHOMONAS VAGINALIS is believed to be pathogenic by most physicians.[1, 2, 3] The resultant vaginitis is one of the most common and the most troublesome conditions seen by gynecologists; in fact, it is becoming more and more of a nuisance because of the difficulty in eradicating the Trichomonas from the vagina with any degree of success.

The most successful treatment for *Trichomonas vaginalis* vaginitis has been based on a lowering of the pH (hydrogen ion concentration) of the vagina to 1.8 to 2.2, and holding it near that pH for 4 to 10 days. At this pH, *Trichomonas vaginalis* cannot survive.

The Significance of the pH

Acidity and alkalinity have long been recognized as important factors in practically all branches of research and industrial work. Sugar manufacturers and refiners, electroplaters and electrotypers, paper manufacturers, sanitary engineers, agriculturists, bacteriologists, biologists, pathologists, chemists, pharmacists, drug manufacturers, and others have used various methods for detecting and controlling acidity and alkalinity, since they have learned by experience that this factor has a very marked effect on the yield and quality of their products, the efficiency of the manufacturing of various materials, the growth of bacteria, and the diagnosis of diseases.

The degree of acidity, corresponding to various pH values, is important and should be mentioned. A solution that has a pH value of 5.0 is 10 times as acid as one with a pH of 6.0; analogously, a solution of pH 4.0 is 10 times as acid as one of pH 5.0; pH 3.0 is 100 times as acid as pH 5.0; thus, 4.0 indicates an acidity 100 times as great as one of pH 6.0; pH 3.0 is 1,000 times as acid as pH 6.0 and 10,000 times as acid as pH 7.0, 100,000 times as acid as pH 8.0, and 1,000,000 times as acid as pH 9.0; *pH 2.0 is 10,000,000 times as acid as pH 9.0* (Table II), the highest pH that may be encountered in the vagina. One can now visualize the value of an acid vaginal medication* which has a pH of 2.0 and which is known to be very destructive to vaginal pathogens, yet does not harm or burn the vaginal mucosa (Table I).

At this very high acidity (pH 1.8 to 2.2), the normal vaginal epithelium is stimulated to grow back to the normal adult thick or resistant stage and desquamated vaginal epithelial cells and debris are liquefied and destroyed.

*Trimagill, S. E. Massengill Company, Bristol, Tenn.

TABLE I. RELATIONSHIP OF THE DEGREE OF ACIDITY OF VARIOUS VAGINAL pH VALUES

pH VALUE		NO. OF TIMES THE ACIDITY EXCEEDS THAT OF AN ULCERATED VAGINA
9.0	Ulcerated vagina, the highest pH recorded in the vagina	1
8.0		10
7.0		100
6.0		1,000
5.0		10,000
4.0	Normal vaginal pH ranges between 3.5 and 4.2	100,000
3.0		1,000,000
2.0	The low pH medication	10,000,000

A similar relationship holds on the alkaline side of the scale; that is, a solution which has a pH of 9.0 is 10 times as alkaline as a solution with a pH of 8.0 and so forth. This relationship is shown in Table II, in which the pH 7.0 is given as a value of 1.

TABLE II. RELATIONSHIP OF DEGREES OF ACIDITY AND ALKALINITY TO pH VALUES

pH VALUE	NO. OF TIMES ACIDITY OR ALKALINITY EXCEEDS THAT OF PURE WATER (pH 7.0)	
0	10,000,000	
1	1,000,000	
2	100,000	
3	10,000	(Acidity)
4	1,000	
5	100	
6	10	
7	1	(Pure water)
8	10	
9	100	
10	1,000	
11	10,000	
12	100,000	
13	1,000,000	
14	10,000,000	

This method of expressing H ion concentration is very inconvenient and clumsy. Sorenen, therefore, suggested the use of the term *pH*, the pH value being the logarithm of the reciprocal of the hydrogen ion concentration. Thus

$$\text{pH} = \log \frac{1}{(\text{H}^+)}$$

Just as an acid solution is said to be normal when it contains 1 Gm. of ionizable hydrogen per liter, so a solution is said to be normal with respect to hydrogen ions when it contains 1 Gm. of ionized hydrogen per liter, since

$$\frac{1}{(\text{H}^+)}$$

is the reciprocal of the normality of H ions in a solution. The pH value can also be defined as the logarithm of the denominator expressing the normality of H ions such as N/10, N/100, N/1,000, et cetera.

Patient A. B., a Negro woman, aged 28 years, was seen at the outpatient Leucorrhea Clinic. A fresh smear was 4 plus for *Trichomonas vaginalis*. The entire field was loaded with this protozoan. There were many bacilli and cocci, both gram positive and negative, present in the gram-stained smear. There were no fungi or Döderlein bacilli present, and the vagina was Grade III to IV (the vaginal pH ranged from 4.9 to 5.6 in Grade III and from 5.6 to 6.3 in Grade IV).

She was not treated, but asked to return to the clinic weekly. She was instructed not to use any vaginal medication, not to have coitus, and not to take a douche. During this entire study the patient never came to the Leucorrhea Research Clinic with an acute vaginitis.

In this study, an old style Beckman electric battery type pH meter with a special curved vaginal electrode was used to determine the pH of the vagina. The pH was determined on one area in the posterior and one area on the anterior fornix. These pH readings were copied from the pointer on the pH scale. Starting in the right lateral fornix, the pH was read from this area, then the tips of the electrodes were moved toward the introitus for 4 to 5 or less millimeters and the pH reading of this area was observed on the pH meter, then the tips of the electrode were picked up and moved 4 to 5 more millimeters toward the introitus and the pH of the area read. This procedure was repeated over and over along the right lateral wall from the fornix to the introitus. The same procedure was repeated at different areas on the left vaginal wall. This was a slow way to determine the pH of the vaginal walls and of the secretion (moist layer) covering the vaginal walls but it was the best that we had at that time.

The Beckman pH machine was calibrated every morning before being used with standard buffered acetic acid solution, pH 4.64.

There were 255 consecutive pH readings of the right and left lateral vaginal walls over a period of 143 days. The pH of each area and the averages are given in Table III.

TABLE III. AVERAGE RESULTS OF 255 CONSECUTIVE pH READINGS OVER A PERIOD OF 143 DAYS IN A CASE OF UNTREATED *Trichomonas Vaginalis* VAGINITIS

DAYS BETWEEN pH READINGS	AVERAGE pH DAY OF					DAY OF CYCLE	REMARKS
	P.F.	A.F.	L.L.W.	R.L.W.	ALL AREAS		
0	5.21	5.27	5.28	5.15	5.25	9th	Itching 2 or 3 days before menses. No itching during menses. Itching 4 days after menses
14	5.62	5.37	5.68	5.48	5.54	23rd	
15	5.43	5.31	5.03	5.38	5.26	11th	
7	5.32	5.30	5.40	5.30	5.33	18th	
7	5.48	5.69	5.61	5.63	5.69	1st	Slight itching
17	6.32	6.22	6.09	5.91	6.13	8th	Itching after menses
27	6.54	6.39	5.61	5.52	6.01	15th	
7	5.48	5.49	5.59	5.32	5.47	21st	
14	5.26	5.38	5.18	5.21	5.26	9th	
7	5.53	5.70	5.48	5.41	5.53	16th	
21	5.22	4.99	5.01	5.03	5.06	10th	
21	5.78	5.80	5.55	5.81	5.73	7th	
21	5.79	5.66	5.50	5.61	5.64	23rd	
Average	5.63	5.42	5.72	5.45	5.54		

Average pH of all posterior fornices	5.63
Average pH of all anterior fornices	5.42
Average pH of all left lateral walls	5.72
Average pH of all right lateral walls	5.45
Average pH of all areas	5.54

In this special *Trichomonas vaginalis* vaginitis case with the battery type of pH machine, the pH of the posterior fornix was 5.63, of the anterior fornix 5.42, of the left lateral wall 5.45, and the average pH of all areas was 5.54. With the new accurate electronic pH machine the pH is 0.4 to 0.6 lower, but the pH would still be in the 4.99 to 6.0 range. This is the pH range of most *Trichomonas vaginalis* infestations which are seen by physicians today.

Trichomonas vaginalis infection in this case and in all *Trichomonas vaginalis* vaginitis cases is found to be in a *hypoacid vagina.* Thus, one might

rationally conclude that acid preparations which are to be used in the vagina especially for the treatment of *Trichomonas vaginalis* infestations should be correctly acidified and correctly buffered.

Electronic pH Studies of the Vaginal Walls Infected With Trichomonas vaginalis

With the advent of electronic discoveries, the physicists developed an ultra scientific method for determining the vaginal pH and a machine which records the pH on a large continuous sheet of pH paper. The tips of the very small electrodes are moved along the vaginal walls and the machine* makes a continuous record of the entire wall, not one spot here and one spot there as with the older battery type pH machine. Also the older battery type machine required a continuous stream of saturated solution of potassium chloride to be flowing over and into the area where the pH was being determined. With the new electronic pH machine no solution is needed in the area in which the pH is being determined. The electronic machine eliminates this "dilution error" which occurs with the battery type pH machine. It is important that this dilution factor be eliminated if accurate vaginal pH recordings are desired.

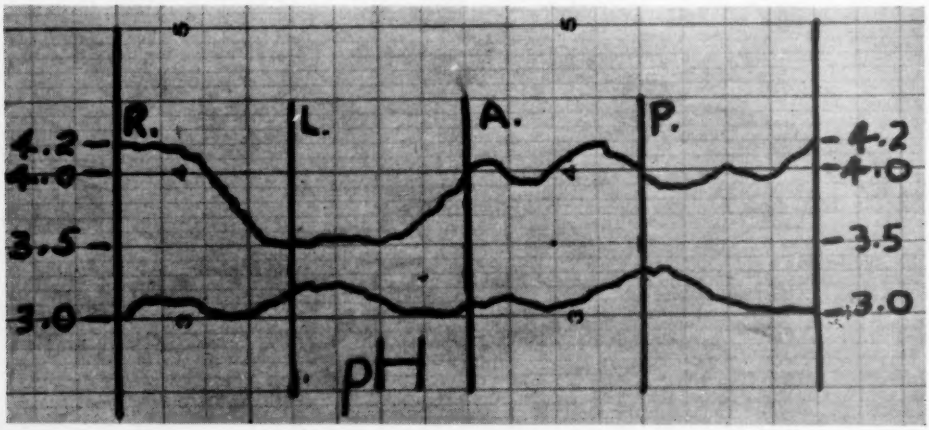

Fig. 1.—The normal vaginal pH as recorded by an electronic pH machine. This pH has been recorded in virgins regardless of age, even near the menopause. The normal vagina varies between 3.0 and 4.2. In most patients with normal vaginas the pH varies between 3.5 and 4.2. The capital letter *R* indicates the right lateral vaginal wall from the fornix to the mucocutaneous junction; *L*, the left lateral wall; *P*, the posterior wall; and *A*, the anterior vaginal wall.

Modern electronic recording machines, with their highly accurate (98 per cent) graph, provide us with the simplest, most precise, and most scientific method of gathering and preserving in writing pH data on vaginal, cervical, uterine, tubal, intraperitoneal, or any moist cavity, and the effects of heat, cold, and drugs on the pH of the vagina or any organ before, during, and after medication is administered. The expression of hydrogen ion concentration in the vagina is an important gauge in the study of the normal and pathologic physiology of that organ.

The vaginal pH can be used to indicate: (a) the amount of glycogen in the vaginal epithelium and glucose in the vaginal secretion (which varies with the amount of active estrogen and/or progesterone, glycolytic enzymes, vitamin B complex, vitamin C, and trace elements in the circulating blood), (b) the height of the vaginal epithelial cells, (c) the type of bacterial flora present

*Minneapolis-Honeywell electronic pH machine.

(Döderlein or mixed or no Döderlein bacilli), and (d) pathologic conditions present. In the vaginal "moist layer" and within the vaginal epithelial layer during the reproductive period, the higher the pH (larger the pH number), the more pathologic changes are likely to be found in the "moist layer," and within the vaginal epithelial layer. In the diseased vagina, the following are present: hypoacidity, hypoglycogen, hypoglucose, "hypo-epithelial cell height," and "hypo-Döderlein bacilli flora."

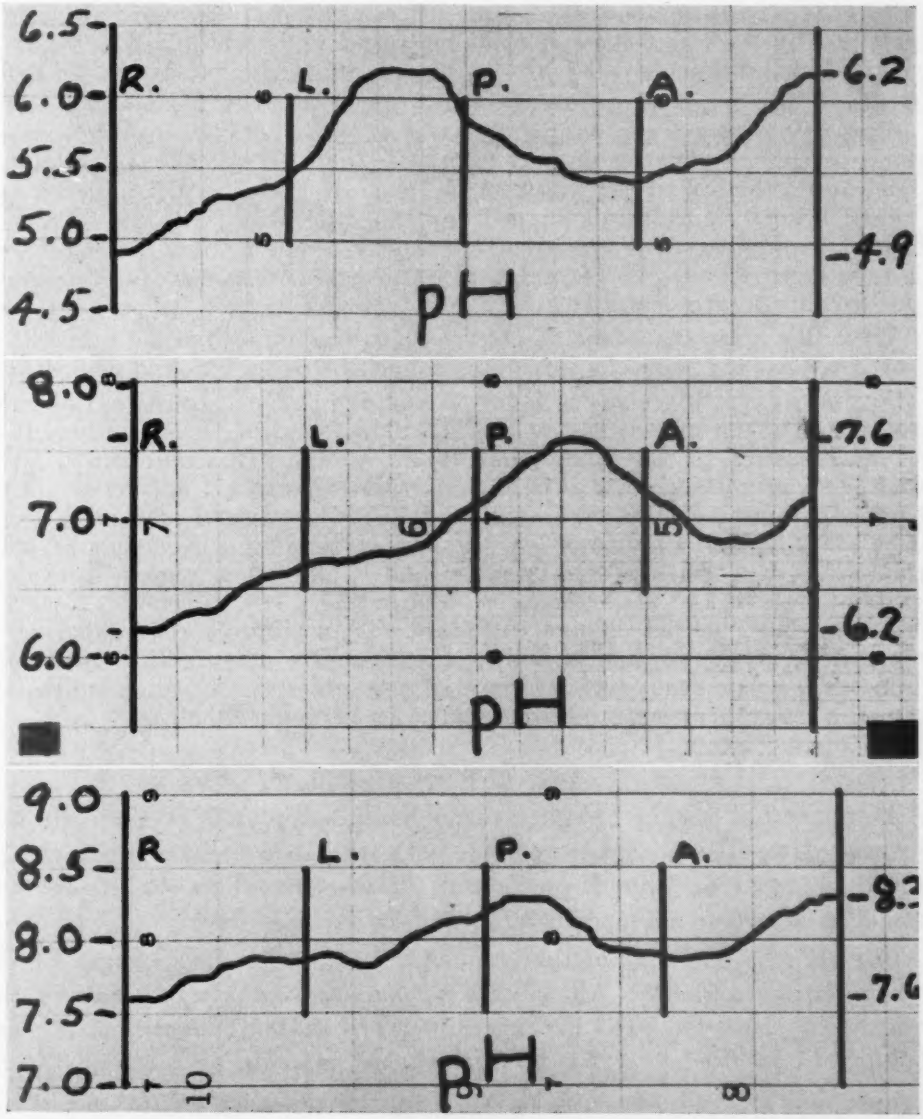

Fig. 2, *A*, *B*, and *C*.—The pH of the vagina infected with *Trichomonas vaginalis* varies from pH 4.99 to 8.3. In approximately 85 per cent of cases the pH is near pH 5.5 as seen in *A*. In acute vaginitis due to *Trichomonas vaginalis* the pH varies between 6.3 and 7.6 as seer in *B*. This pH range is not often found in vaginas infested with this protozoan.

With the advent of the electronic pH machine which was used in the present study, the pH of (1) vaginal secretions ("moist layer"), which cover all vaginal epithelial walls, and (2) the vaginal epithelial surfaces of the entire

vagina, from the fornix to the vaginocutaneous junction, can be recorded in writing and then compared with previous recordings on the same vagina or with another vagina with another infection or with the same infection.

First, it was necessary to find the pH of the normal vagina. The normal vagina was determined by studying virgins while under anesthesia before or during surgery or virgins who came to the writer's office because of severe dysmenorrhea, or older women who never married. Very small, long, curved electronic pH electrodes were readily passed through the small hymenal openings to obtain continuous vaginal wall pH recordings. The normal vagina, as determined by the electronic pH machine, was found to be pH 3.5 to 4.2. The normal pH has been recorded in virgins, at different ages, as low as pH 3.00 (Fig. 1).

The electronic pH was recorded on the vagina of 1,500 consecutive private patients with various pathologic conditions. In the *Trichomonas vaginalis* infected vagina the lowest pH was 4.99 and in most cases the pH ranged between 5.0 and 6.2 until vaginitis developed and then the pH rose to pH 6.3 up to as high as 7.5 and 7.6. This was the pH range in every acute Trichomonas vaginitis infection. Above pH 7.6 and on up to 8.0 and 8.3, ulcerative Trichomonas vaginitis lesions were observed.

With this accurate scientific electronic pH machine it was found that the pH of *Trichomonas vaginalis* infections ranged between 4.99 and 8.30 (Fig. 2).

Several interesting observations were made in regard to the pH of vaginal secretions covering all vaginal epithelial surfaces, which I have designated as the "moist layer." It was found that, if the vaginal pH is found to be pH 5.8, and if the vaginal secretion is removed from the vaginal epithelial walls by drying with air or cotton, the resulting pH of the vaginal epithelial surfaces will be more acid, pH 5.0 to 5.2; if the vaginal secretion is removed from the vaginal walls in a Trichomonas infection and is allowed to remain in the air at room temperature, the pH *becomes less and less acid* (the pH moves toward the alkaline side). This pH change will start within minutes after this secretion is removed from the vagina. I believe this is due to putrefaction of chemicals within this Trichomonas secretion, in contrast to normal secretion which if left in the air at room temperature becomes more acid from metabolism.

Summary

An untreated case of *Trichomonas vaginalis* vaginitis is presented in which 255 consecutive pH readings were made with the battery type pH machine over a period of 143 days. The pH readings of *Trichomonas vaginalis* infections with the modern electronic pH machine are also presented.

The pH of a majority of the vaginas infected with *Trichomonas vaginalis* fall between 5.0 and 6.0. All acute *Trichomonas vaginalis* infestations range just above or just below pH 7.0. Several new observations about the pH changes of leukorrhea (moist layer) due to *Trichomonas vaginalis* are presented.

References

1. Karnaky, K. J.: Obst. & Gynec. 5: 93, 1955.
2. Karnaky, K. J.: Am. J. Obst. & Gynec. 71: 391, 1956.
3. Karnaky, K. J.: Mississippi Valley M. J. 76: 60, 1954.

2614 Crawford Street

TREATMENT OF VULVOVAGINITIS WITH A NEW COMBINATION OF NITROFURANS

JAMES E. ENSEY, M.D., DALLAS, TEXAS

VULVOVAGINITIS, caused by *Trichomonas vaginalis, Candida albicans, Hemophilus vaginalis,* or other bacteria, is still the commonest gynecologic office problem. Although diagnosis is usually easy and response often prompt following treatment with any of a variety of medicaments such as dyes, heavy metal preparations, sulfonamides, antibiotics, quinolines, and surface-active compounds, cases of chronic or mixed infection are often extremely difficult to cure. In recent years, we have been obtaining good results with two preparations containing the synthetic antimicrobial nitrofurans, (1) nitrofurazone (Furacin*) and furazolidone (Furoxone*). Furacin vaginal suppositories are useful to prevent or treat infection following gynecologic surgery or radiation treatment, but unfortunately ineffective against either *Trichomonas vaginalis* or *Candida albicans.* The other nitrofuran, Furoxone, is both trichomonacidal and bactericidal, and we have found its clinical dosage form, Tricofuron,* of considerable value in simple trichomoniasis. Furoxone, however, has no effect on fungal infections. A nitrofuran possessing potent antifungal action has now been added to Tricofuron vaginal suppositories and powder. This is nifuroxime (Micofur*) anti-5-nitro-2-furaldoxime. We have been conducting clinical studies on the combined preparation (Tricofuron Improved*) and the present report summarizes our experiences with it.

Material and Methods

Of the 75 office or consultation patients treated, most had acute exacerbations of otherwise uncomplicated vulvovaginitis caused by either *T. vaginalis, C. albicans,* or mixed infections with both these organisms.

Tricofuron Improved is available in 2 dosage forms: the vaginal powder (containing 0.1 per cent Furoxone and 0.5 per cent Micofur) and the vaginal suppositories (0.25 per cent Furoxone and 0.375 per cent Micofur).

Uncomplicated Vulvovaginitis.—Of the 75 patients with this condition, we found *T. vaginalis* to be the apparent cause in 48; *C. albicans* was present in 19, while 8 had a mixed infection with both these organisms. The latter group includes the only 2 cases in which *Hemophilus vaginalis* was also observed. Virtually all of our cases were chronic and previous treatment with various topical or systemic drugs had been administered for this condition. The duration of symptoms ranged from 1 month to 18 years.

When treatment was begun and at each subsequent visit, a drop of the vaginal secretion was examined by the wet-drop technique and gram-stained smear. If no organism could be identified, the material was cultured for *T.*

*Eaton Laboratories, Norwich, N. Y.

vaginalis and *C. albicans*. We use the STS (simplified trypticase serum) agar with penicillin and dihydrostreptromycin to culture the flagellate, and Nickerson's medium for the yeast. We did not culture for *H. vaginalis*, relying rather on the presence of "clue cells" and small gram-negative pleomorphic bacilli in several wet mounts.

Following preliminary thorough cleansing and drying of the vagina and external genitals, all patients received an insufflation of Tricofuron Powder Improved during each visit. They were supplied with a sufficient quantity of the Tricofuron Suppositories Improved to last them until the next weekly visit, and instructed to insert one suppository into the posterior fornix every morning and night, following douches of mild vinegar solution. Treatment was carried out throughout the menses when suppositories were inserted with the aid of a tampon.

Most of the patients were seen at least once a week, at which time the subjective progress was recorded and the patient was queried as to any side reactions from the drug. The microscopic examination was then repeated, and material for culture was taken if the findings on direct examination were negative. Treatment was continued until results of at least 3 consecutive weekly examinations were negative, by both wet drop and culture. If findings were still positive after 6 weeks' treatment the case was recorded as a failure and some other type of medication used.

Male Trichomoniasis.—Of the 56 patients with *T. vaginalis*, 49 were married. In all cases where a marital cross-infection with *T. vaginalis* was suspected, we urged the patient to bring her husband for examination and possible treatment. Probably because the infection in the male is usually asymptomatic, our plea was not always successful. Marital infection was suspected in all of the married patients, and 21 husbands of 34 examined were found positive for Trichomonas, but 7 refused treatment (Table I). Of the 14 husbands who were treated, 2 received a course of aminitrozole (Tritheon*), 100 mg. orally three times a day for 10 days and the other 12 were treated with nitrofurantoin (Furadantin†), 100 mg. orally four times a day for 10 days. All male patients were queried as to symptoms at each visit, and prostatic secretions, material from the preputial sac, urethral smear, and urinary sediment were examined microscopically by the wet-drop technique, and if the result of the microscopic examination was negative, by culture. The clinical diagnosis in the 14 husbands who were treated was trichomonal prostatitis.

TABLE I. TRICHOMONAS VAGINALIS IN 49 HUSBANDS OF PATIENTS WITH VAGINAL TRICHOMONIASIS

	HUSBANDS EXAMINED		HUSBANDS NOT EXAMINED
	POSITIVE FOR *T. vaginalis*	NEGATIVE FOR *T. vaginalis*	
Treated with Furadantin	12	--	--
Treated with Tritheon	2	--	--
Untreated	7	13	15

Tricofuron Improved in both powder and suppository form was also used in gynecologic patients to prevent infection following cervical cauterization or conization and vaginal plastic surgery. These patients also received antibiotics systemically.

Results

Table II shows the results obtained in our patients with uncomplicated vulvovaginitis.

*Ortho Pharmaceutical Corporation, Raritan, N. J.
†Eaton Laboratories, Norwich, N. Y.

TABLE II. RESULTS OF TREATMENT OF VULVOVAGINITIS WITH TRICOFURON IMPROVED IN 75 PATIENTS

INITIAL ORGANISM	NO. OF PATIENTS	NO. CURED	SYMPTOMATIC CURE BUT CULTURE POSITIVE	RECURRENCE	FAILURE
Trichomonas vaginalis	48	33	12	-	3
Candida albicans	19	19	--	-	-
T. vaginalis and C. albicans	8	4	2	2	-
Total	75	56	14	2	3

Symptomatic improvement was observed within one week of the beginning of treatment in all but 7 patients whose husbands refused examination or treatment. Of the 14 patients who still harbored *T. vaginalis* at the end of the treatment, 12 presumably were being reinfected by their husbands. The 2 patients who later had recurrences had at first shown rapid symptomatic improvement and the vaginal secretions became microscopically and culturally negative; after 2 weekly visits they had relapses, probably because of reinfection by their husbands who refused treatment.

C. albicans infection was easily eliminated in all our 19 patients, including both those in whom it was present alone and the 8 patients in whom it was present in association with *T. vaginalis*. *Hemophilus vaginalis* was eradicated promptly in the 2 patients with triple infection, but *T. vaginalis* recurred probably because of reinfection by the husbands.

Urinary trichomoniasis in the husbands who were treated orally with Furadantin was cured in all 12 cases so treated. The 2 husbands treated with Tritheon were also cured. There were no side effects with either medication.

Equally good results were obtained with Tricofuron Improved following gynecologic procedures, with rapid healing and only limited serosanguineous vaginal discharge, slough, and local reaction. It is probable that many postoperative infections include *T. vaginalis* and fungi in addition to the common pathogenic bacterial flora.

The patient acceptance of Tricofuron Improved Powder and Suppositories was good throughout. We failed to encounter any instance of local or systemic intolerance or other adverse reaction to this medication.

Comment

Our experiences with Tricofuron Improved show the necessity of eliminating marital infection in women with trichomonal vaginitis. Of our 19 patients in whom trichomonads persisted at the end of the treatment, the failure was considered due to marital reinfection in all but one case. The results with *T. vaginalis* in our series are comparable to those reported with Tricofuron by other clinicians.[2-5] Our experience with the 12 husbands treated orally for trichomoniasis with Furadantin also agrees with the results in previous reports indicating that Furadantin is trichomonacidal both in vitro[6, 7] and clinically by peroral administration in patients with urinary trichomoniasis.[2, 3, 8, 9]

The addition of a specific antifungal agent to Tricofuron is, in our view, a definite improvement over the original preparation. Mixed infections are generally considered to form only a small proportion of cases of uncomplicated vulvovaginitis but, in many cases where the disease becomes recurrent or chronic, different organisms are isolated in the same patient at various times. Candida vulvovaginitis may often follow vaginal trichomoniasis,[10] especially if treated with a purely antitrichomonal agent.[11] A larger prevalence of mixed

infection than is commonly assumed may also be the cause of the current controversy about the frequency of various organisms; while the majority of clinicians find that *T. vaginalis* is the most frequent agent,[10, 12] others concentrating on detection of *C. albicans* find this fungus 7 times as frequently as the flagellate, the yeast being reported in many cases where *T. vaginalis* was originally believed to be involved.[13] Still other clinicians[14, 15] report that the most frequent pathogen is *H. vaginalis.* This may indicate that mixed infection, probably often subclinical, is present most of the time and that the organisms isolated during any exacerbation represent merely the species predominating at the moment. To succeed, the topical preparation used should possess sufficient activity to eliminate trichomonads, fungi, and any associated pathogenic bacteria, such as *H. vaginalis.* In our experience, the results in the treatment of trichomonal, monilial, or mixed vulvovaginitis with Tricofuron Improved compare favorably with those we obtained with any other common drug preparation including hexetidine (Sterisil*), nystatin (Mycostatin†) alone or with tetracycline hydrochloride (Mysteclin†) as well as older preparations such as gentian violet.

Summary

Tricofuron Improved was used in suppository and powder form in the treatment of 75 patients with severe vulvovaginitis caused by *Trichomonas vaginalis* in 48 patients, *Candida albicans* in 19, or both these organisms in 6, or both in association with *Hemophilus vaginalis* in 2. Permanent cure by both laboratory and clinical criteria was achieved in 56 within an average of 6 weeks' treatment. An additional 14 patients became asymptomatic but not microscopically cured of *T. vaginalis* vaginitis; in all of these cases the husband refused treatment. There were 3 complete failures of therapy. The husbands of 34 women with trichomonal vaginitis were examined; 21 were found to have genitourinary trichomoniasis, but 7 refused treatment. Of the other 14 husbands, all with trichomonal prostatitis, 12 were treated orally with Furadantin and 2 with Tritheon with good results. There were no toxic or allergic side reactions to medication.

References

1. MacLeod, P. F., Rogers, G. S., and Anzlowar, B. R.: Internat. Rec. Med. & G. P. Clinics **169**: 561, 1956.
2. Schwartz, J.: Obst. & Gynec. **7**: 312, 1956.
3. Schuppius, A.: Med. Klin. **52**: 894, 1957.
4. Martinez-Lara, C.: Rev. conf. med. panam. **4**: 58, 1957.
5. Cueva-Bastarrachea, R.: Thesis, 1956 Lima, Peru, Universidad nacional Mayor de San Marcos, Facultad de medicina.
6. Mintzer, S., Kadison, E. R., Shlaes, W. H., and Felsenfeld, O.: Antibiotics & Chemother. **3**: 151, 1953.
7. Rogers, G. S., Belloff, G. B., Paul, M. F., Yurchenco, J. A., and Gever, G.: Antibiotics & Chemother. **6**: 231, 1956.
8. Hasen, H. B., and Moore, T. D.: J. A. M. A. **155**: 1470, 1954.
9. Bisquertt-Torres, J.: Rev. chilena urol. **19**: 130, 1956.
10. Lang, W. R., Stella, J. G., and Benchakan, V.: Obst. & Gynec. **8**: 364, 1956.
11. Thomas, H. H.: Obst. & Gynec. **9**: 163, 1957.
12. Perl, G., Guttmacher, A. F., and Raggazzoni, H.: Obst. & Gynec. **7**: 128, 1956.
13. Pace, H. R., and Schantz, S. I.: J. A. M. A. **162**: 268, 1956.
14. Ray, J. L., and Maughan, G. M.: West. J. Surg. **64**: 581, 1956.
15. Gardner, H. L., and Dukes, C. D.: Am. J. Obst. & Gynec. **69**: 962, 1955.

310 Preston Royal
Medical Center

*Warner-Chilcott Laboratories, Morris Plains, N. J.
†E. R. Squibb & Sons, New York, N. Y.

THE NATURE OF THE "PERINUCLEAR HALO": FURTHER CLINICAL, CYTOLOGICAL, AND PATHOLOGICAL STUDIES

NURI SAĞIROĞLU, M.D.,* MIAMI, FLA.

(From the Cancer Institute at Miami, Cancer Research and Cytology Center)

MEDICAL cytology has made a great impact on the over-all problem of cancer, especially in early detection and prevention of the disease. The studies and observations of human cells made by cytologists, pathologists, and biochemists in many sections of the world have resulted in discoveries that today are playing significant roles in the never-ending search to learn more about the origin and nature of cancer cells. Morphocytologic studies have also proved to be a valuable adjunct to physicians because, using this method, the investigator is able to observe cellular abnormalities which are not apparent through the histological examination of tissues.[5, 6]

Many facts are still unknown in cancer cytology—the science is so young it has barely emerged from the "swaddling" stage—and some established cytological findings require amplification and clarification. An excellent example is the problem of the "precancer cell complex"—a cell entity that has been discussed widely and sometimes rather heatedly.[3]

The precancer cell complex, studied and originally described by Ayre,[1] has been accepted by many physicians and cancer researchers as a cytological entity but, as such, it has been doubted by some groups of cytologists and pathologists. Some researchers have preferred to classify this stage of cellular development as: anaplasia, atypical hyperplasia, dysplasia, precancerous metaplasia, or restless epithelium. Papanicolaou[7] and some others have labeled such cell groups as dyskaryosis.

The precancer cell complex, as the name indicates, is composed of cells which represent a possible transitional stage between normal and cancerous cells, yet this designation has not been accepted by all physicians, perhaps because the word *precancer* may have created a negative effect on them and their patients.

The purpose of this paper, however, is not to discuss the appropriate title of this particular cytological entity, nor to study it, but to endeavor to analyze an intimately related subject: the occurrence of the perinuclear halo. This subject has recently received recognition and gained in importance, primarily as a result of the extensive discussion and presentation of various viewpoints of numerous cancer investigators. One of these, Ayre[2] who first described and

*Formerly Assistant Gynecologist and Obstetrician in the First Clinic of Obstetrics and Gynecology of the University of Istanbul, Turkey.

illustrated the perinuclear halo, has accepted it as important evidence corroborating the precancer cell complex. Two other cancer investigators, Koss and Durfee,[6] have established a special category for cases showing cells with perinuclear halos which they have labeled *koilocytotic atypia.*

Recent studies seem to indicate that the perinuclear halos observed in smears from the stratified squamous epithelium of the uterine cervix are the result of artifacts.[10]

A secondary purpose of this paper is to show the clinical, cytological, and pathological evidences gained from cases showing perinuclear halos and to present drawings and photomicrographs taken from the cytological and pathological slides involved as evidence substantiating the theory that the perinuclear halo under discussion is a result of artifacts.

Material and Method

Slides were made of material taken from 109 cases, cytologically diagnosed as inflammatory or with precancerous cell changes, found among research patients of the Cancer Institute, Cancer Research and Cytology Center, Miami, Florida.

The material for cell study was obtained with Ayre's wooden spatula and stained in accordance with Papanicolaou's[8] staining technique. In addition, the smears for each case were stained in TMK-101, multicolor dye solution.[9]

In the Papanicolaou staining technique, the smears are first fixed in absolute alcohol and ether. They are then thoroughly washed in concentrated alcohols, then mounted in balsam or permount. (In the Miami Cancer Institute, slides are mounted at a high temperature—more than 200° C.)

In the TMK-101 technique, fresh smears made by spatula are immediately placed in the aqueous solution of the dyes, without fixation. After 15 minutes, the slides are removed from the staining jar, mounted in the same dye solution, and examined under the microscope.

Results

A study of the slides showed that 6 out of 36 inflammatory cases and 27 out of 73 cases with precancerous cell changes—a total of 33 cases—displayed large, clearly outlined halos.*

Clinical Findings.—Seventeen of the 33 patients in whose cells halos were demonstrated revisited the Cancer Institute for periodic control during the study. In 13 cases clinically well-developed, chronic nonspecific cervicitis was found when gynecological examination was made. Clinical information concerning the 16 remaining cases was taken from individual files maintained in the Institute. In the latter cases, the uterine cervix was generally irregular in shape, with erosion and cervicitis. (It can be easily accepted that some of these cases were clinical chronic nonspecific cervicitis.) In the 13 cases which I personally studied, the uterine cervix was usually larger than normal, lacerated, and irregular, and showed petechial bleeding. Some ulcerous or red-and-white areas were also observed. Nabothian cysts were frequently present. Usually there was a mucous discharge, either clear or dirty. These findings are specific clinical evidences of chronic nonspecific cervicitis.

Cytological Findings.—The smears which were scraped from the uterine cervix showed a marked hyperactivity in the superficial cells. Frequently,

*The tiny and narrow perinuclear halos which are shown as a characteristic of Trichomonas infestation and are similarly seen in malignant cells in cytology are not discussed in this paper.

these were larger than normal. Giant cells were particularly noticeable. The nuclei were usually larger and darker than normal. Dumbbell-shaped nuclei and multinucleation were seen frequently. In some of the cells, two different cytoplasmic zones were clearly distinguishable around the nucleus. One zone, darkly stained, occupied the peripheral part of the cytoplasm and usually showed an irregular, sharp, and darkly stained inner border. The other zone,

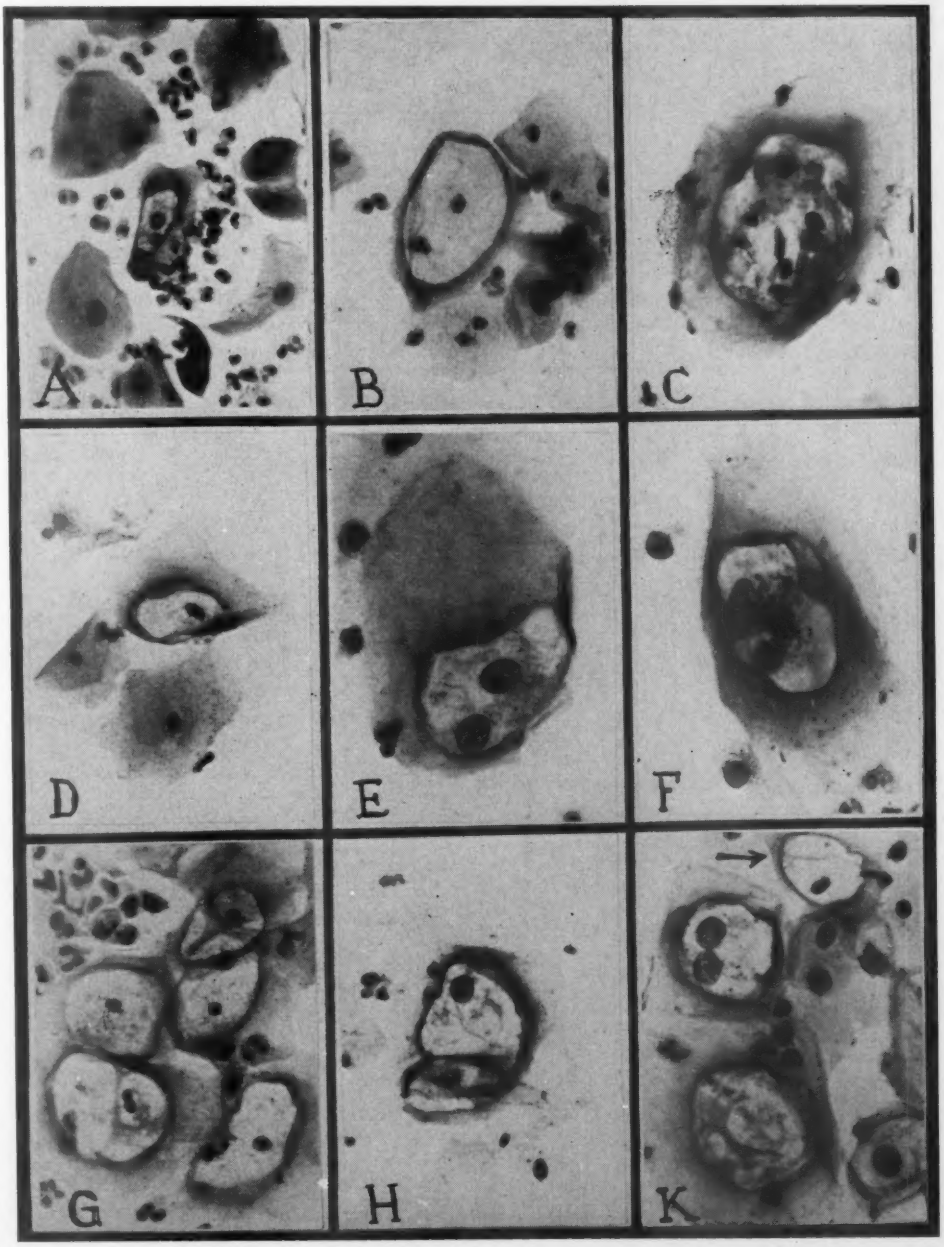

Fig. 1.—Photomicrographs of different types of halos in cervical scraping smears.
A, *B*, *G*, *H*, and *K*, Show well-defined halos.
C and *F*, Show many leukocytes within halo.
D and *F*, Show evidence of membrane defects with irregular and double-torn halo outlines.
E, Eccentric halo.
K, Three cells with halos, one without nucleus.

located around the nucleus, formed the border line of the first zone. The latter or inner area was lighter than the outer part of the cytoplasm. In fact, it was so light that the area appeared empty. This perinuclear zone is known as the *halo*. Papanicolaou[7] calls this area the "perinuclear cavitation." The

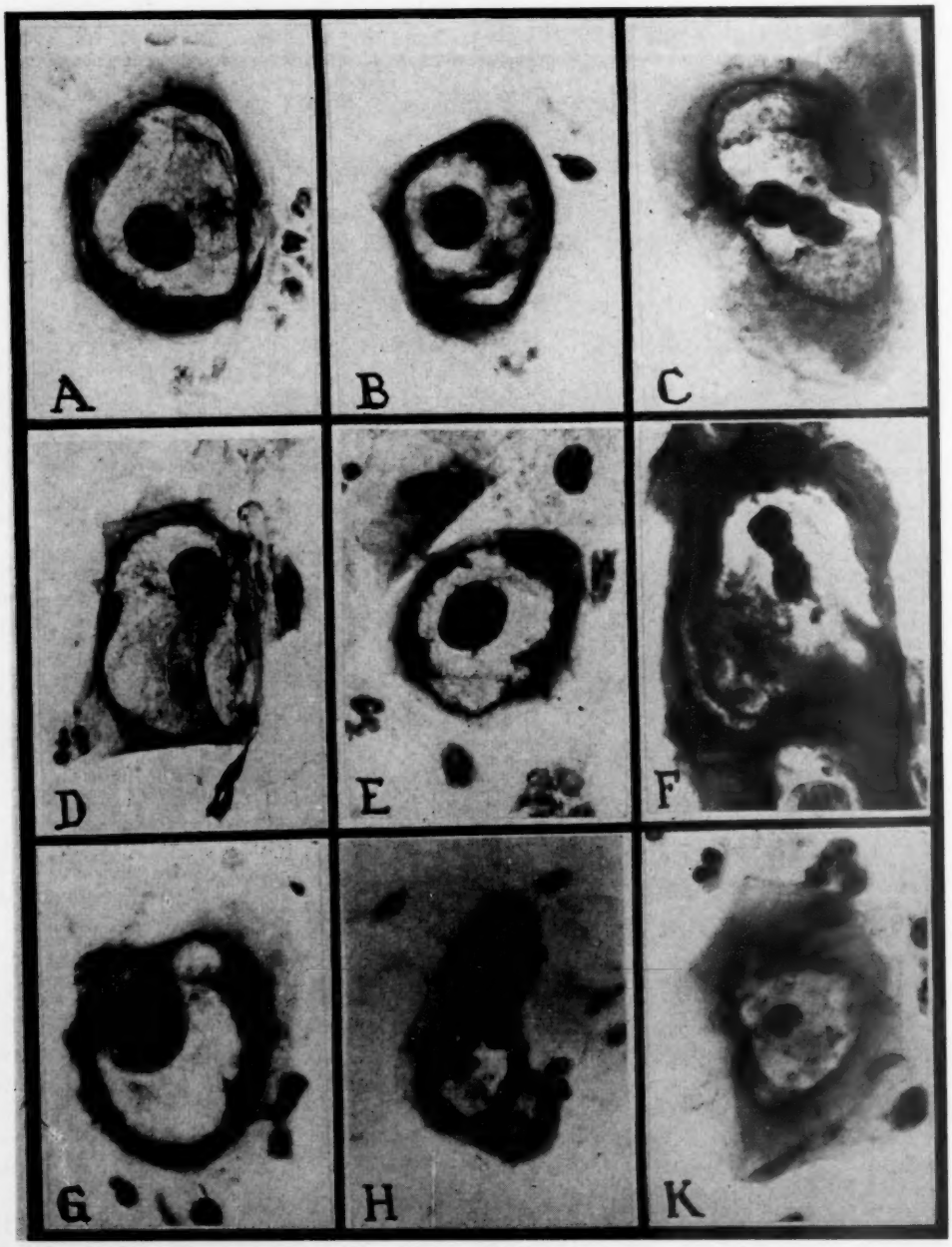

Fig. 2.—Photomicrographs of different types of halos. All of these photomicrographs show evidences of irregular membrane defects. Deeply indented irregular halo borders and naked nuclei and cytoplasm are seen in these halos.

area occupied by the perinuclear zone varied in size and position (Figs. 1-6). In most instances, the clear zone occupied one fourth to two thirds of the total cytoplasmic surface, but at times it was so wide that only a rim of thicker peripheral cytoplasm remained.[6]

The halos in this study, as shown in Fig. 1, *B*, *D*, *H*, and *K*, Fig. 2, *B*, *E*, *F*, *G*, and *K*, Fig. 3, *A*, *D*, and *K*, Fig. 4, *B* and *F*, and Fig. 5, *B* and *C*, are outlined with extreme sharpness in some cells; their borders are thick, dark, and irregular and the surface of the halos is as light as the background of the slide. In some cells, however, the halos show a darker area inside the sharp outline. Usually, such cells are not homogeneous (Fig. 1, *C* and *F*, Fig. 2, *D*, Fig. 3, *E*, and Fig. 5, *G*, *H*, and *K*).

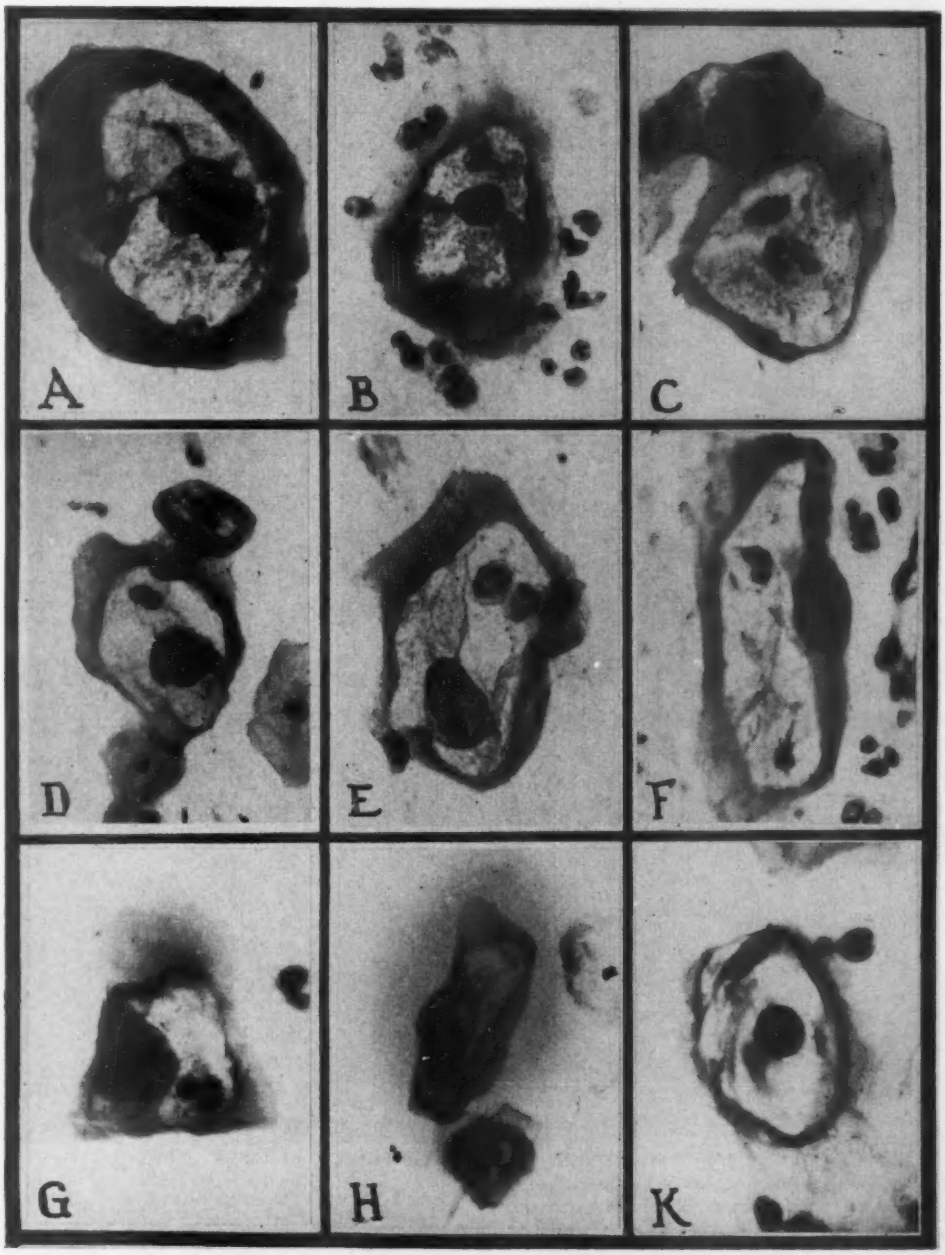

Fig. 3.—Photomicrographs of different types of halos.
A and *B*, Show well-defined halos with irregular, sharp, and dark borders.
E and *G*, Show a leukocyte inside the halo.
F, Shows no nucleus inside halo, but just on the outer rim.
G and *H*, Show the opening of two membrane parts like a lid over the halo.
K, Shows the evidence that the halo is an irregularly torn membrane defect.

With the TMK-101 staining technique, it was occasionally found that some halos have an upper and lower face and that each face is outlined by a

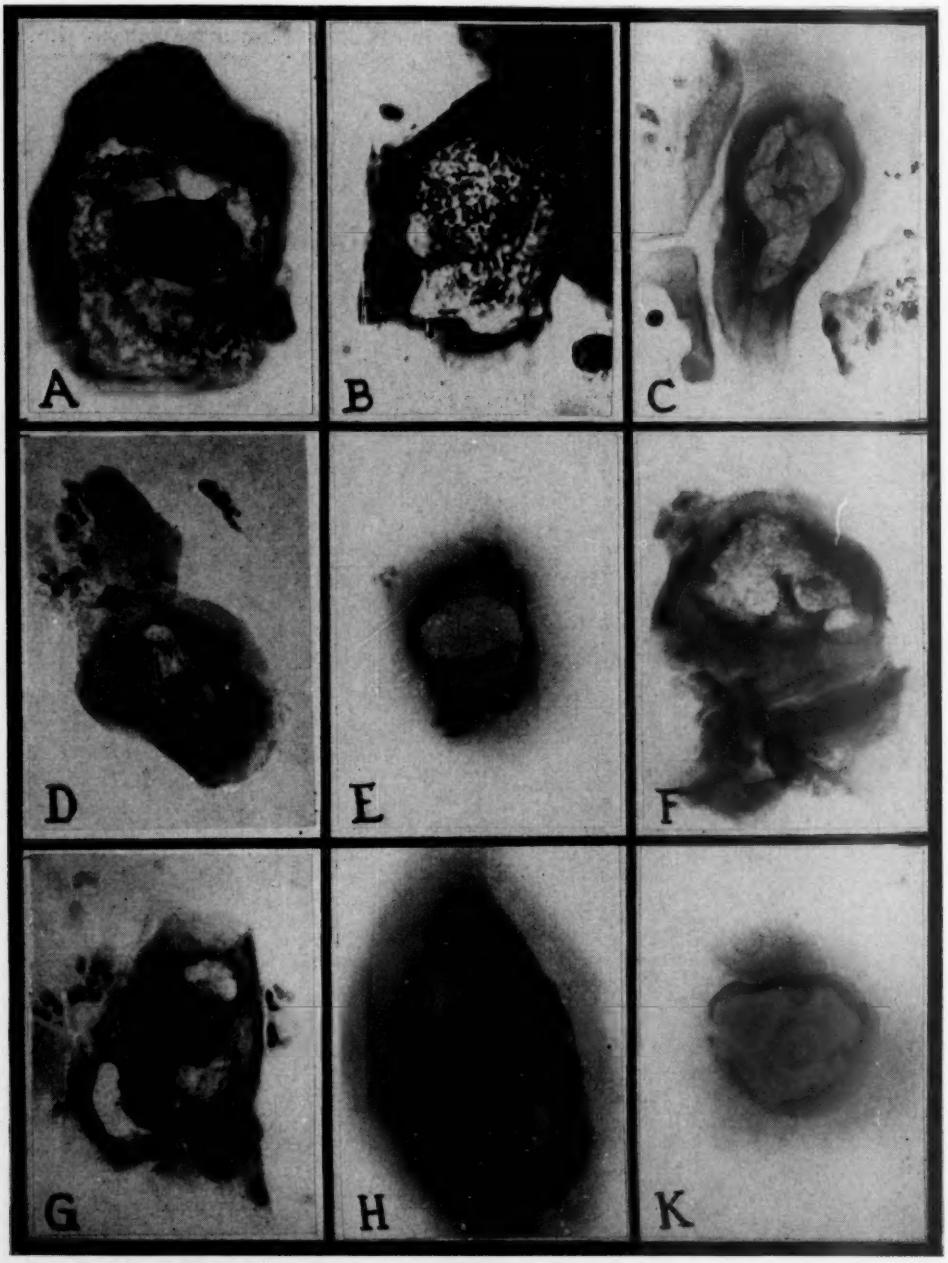

Fig. 4.—Photomicrographs of different types of halos.
A, Well-defined halo, with nucleus inside.
B, Cell with halo which has no nucleus.
(In both *A* and *B* two cells with halos are extremely similar. How can one or two probably hyperactive nuclei leave the cell? The only reasonable answer is "membrane defect.")

different edge which varies in size and shape. No way has yet been discovered for classifying variations of the halos in size and shape. At times, it is a true circle, but at other times it is shaped like an irregular oval. Frequently such

halos are slightly indented, but almost as frequently they are deeply indented (Fig. 2, *B*, *E*, *F*, *G*, and *K*, Fig. 3, *A*, *B*, *C*, and *K*, Fig. 4, *A*, *B*, *H*, and *F*, and Fig. 5, *B*, *C*, *F*, and *G*).

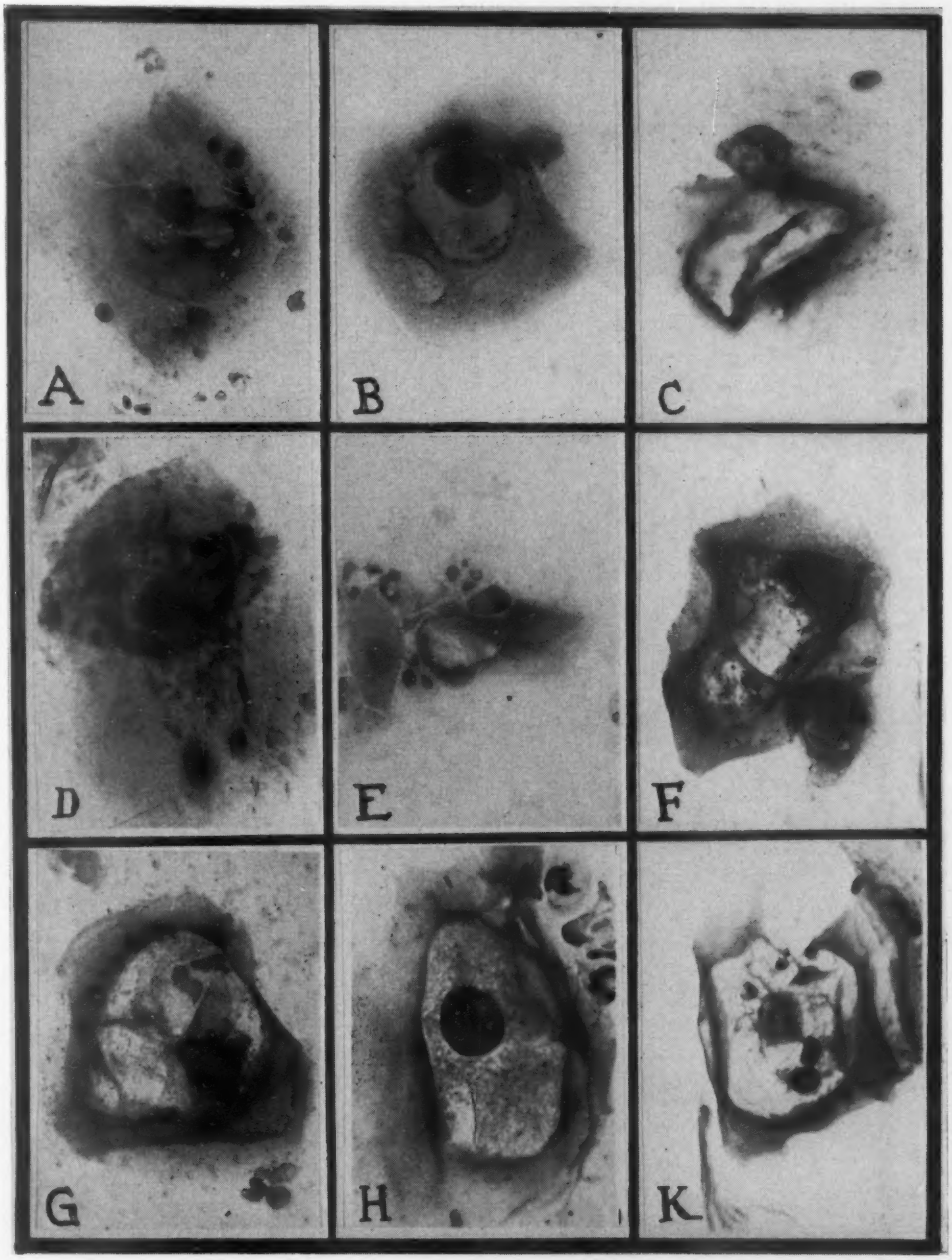

Fig. 5.—*A*, Side view of a cell with halo. The nucleus is standing in the crater of the cell, with no membrane covering it. Compare with Fig. 7, upper *MC*.

B, Evidently shows that halos are produced by membrane defect.

C, A cell with halo which does not show nucleus inside. There is a nucleus outside joined to the halo border, probably belonging to this cell. *F* shows a similar cell.

D, Shows a cell with halo. A seepage of granular material, probably of cytoplasmic content, occurs.

E, A folded cell with halo, the nucleus seen outside of the cell.

G and *K*, Torn membrane parts in halos.

H, Cell with halo, shaved membrane parts attached to border of halo.

Sometimes, the halos are not centrally located with respect to the border of the cell. The edge of the halo may extend right into the outer rim of the cell, the two thus combining into a single border, or the halo may push itself out of and beyond the cell (Fig. 1, *A*, *B*, *D*, *E*, *G*, *H*, and *K*, and Fig. 2, *D*). In some cells which display halos, a part of the cellular membrane appears to stand up, quite like a lid, over the halo (Fig. 3, *G* and *H*, and Fig. 6, *B* with nuclei). The irregular parts remain joined to the edge of the primary halo

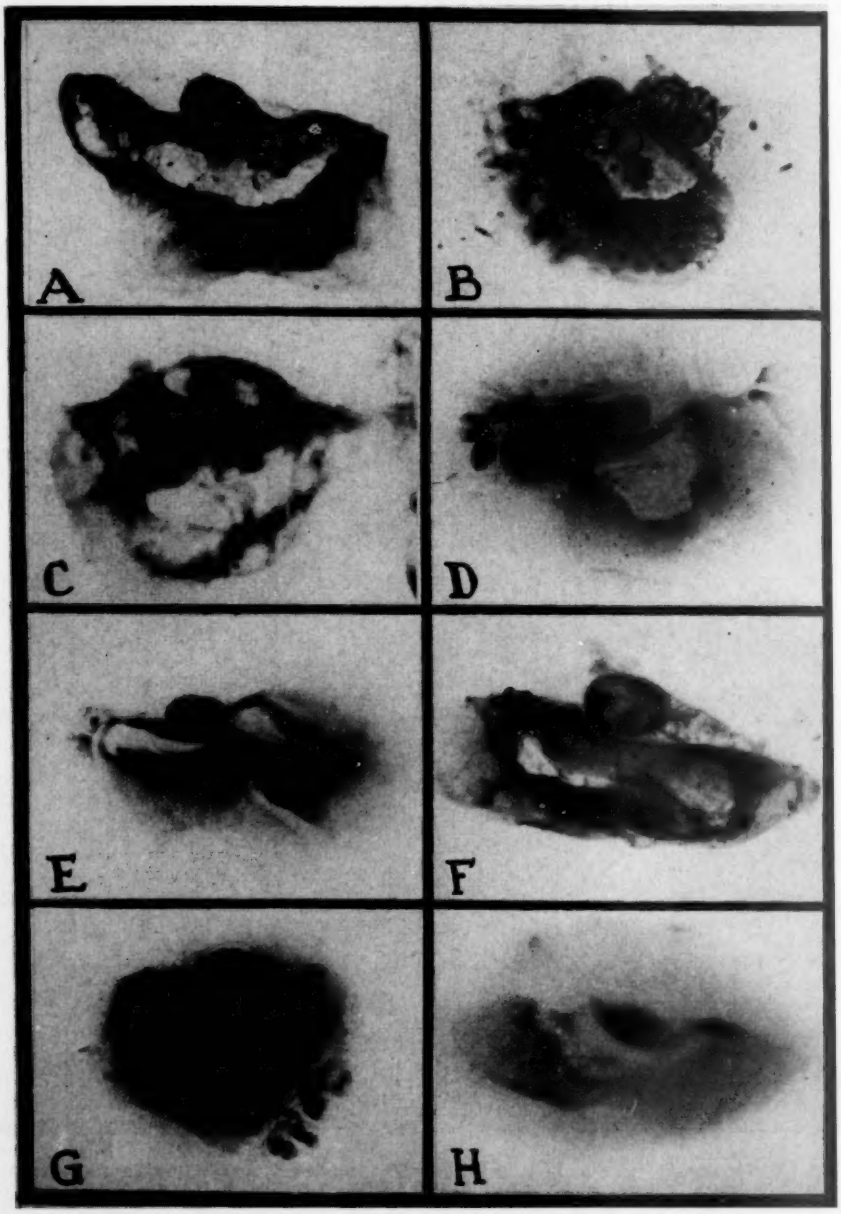

Fig. 6.—Photomicrographs of folded cells with halos. Each has a nucleus half in cytoplasm, half out of cell. No membrane cover is seen on the nuclei. These are the most distinctive evidences of membrane defects.

***A*, The nucleus is "tied" up to its cell only by cytoplasmic filaments.**

***B*, Cell with halo, with no nucleus inside, but it does contain erythrocytes. A membrane and cytoplasm lid with dumbbell-shaped nucleus is opened over the halo.**

***C*, Membrane defect quite like a crater.**

and show a similar border. In some cells, a seepage of granular material occurs—probably of a cytoplasmic content (Fig. 5, *D*). In some instances

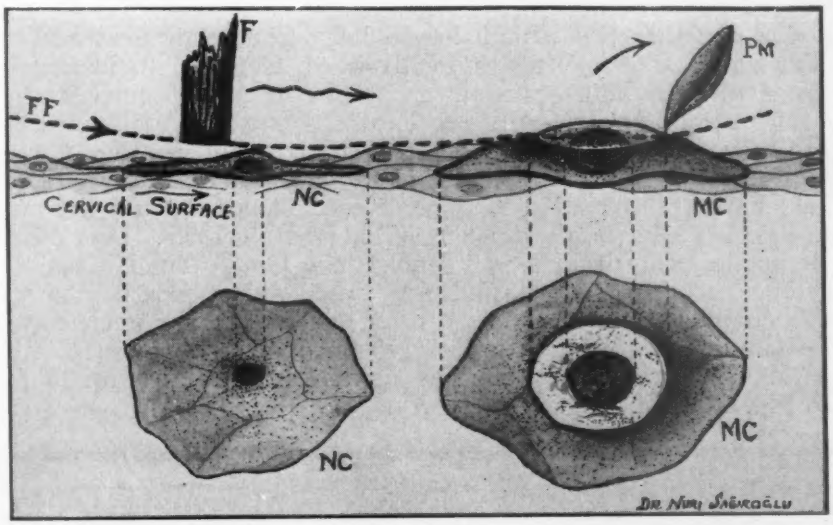

Fig. 7.—Mechanism of a factor producing defects in cells which are in suitable condition.

Upper *NC*, Side view of a normal squamous cell on the surface of the uterine cervix. Lower *NC*, Top view of cell shown in upper *NC*.

Upper *MC*, Cell in suitable condition (hyperactive, edematous, thick, swollen, and macerated dead cell higher than the other cells on cervical surface) is defective after scraping. Lower *MC*. Top view of cell shown in upper *MC*; *PM*, pruned membrane part; *F*, factor or scraper which is scraping the surface of the cervix; *FF*, the direction of the factor is parallel to the surfaces of the cells and of the cervix.

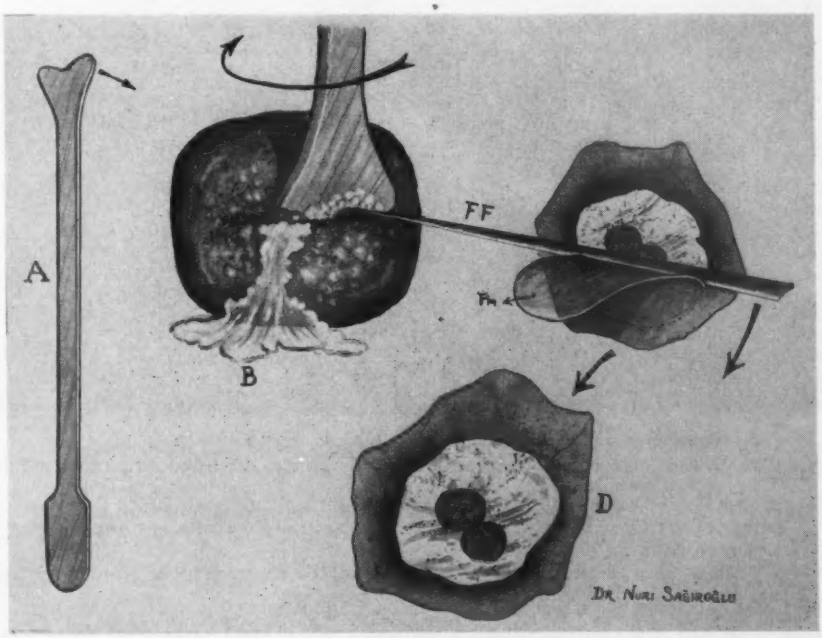

Fig. 8.—Mechanism of production of defect in cell by spatula.

A, Ayre's wooden spatula.

B, Spatula is scraping the cellular material from the surface of the uterine cervix which shows chronic nonspecific inflammation. *FF*, Effective edge of spatula as a rough blade tears away the membrane part of a cell which is in suitable condition. *Pm*, Pruned membrane part of the cell.

D, Cell with membrane defect or crater after scraping. Is this an inner halo?

(Fig. 5, *A*, and Fig. 6, *A* and *C*), the nucleus is seen half in, half out of the folded cell with halo. Fig. 6, *C* especially shows a crater-shaped halo in which the nucleus is standing without membrane covering (compare with Fig. 7, upper *MC*).

Fig. 6 shows the cells with halos folded. Thus they are seen similarly from a side view. The nucleus, especially in *A*, is joined to its cell by cytoplasmic filaments only and, again, no membrane covers the nucleus.

The nucleus or nuclei usually are located somewhere within the halo but seldom are they seen in the exact center (Fig. 1, *B* and *G*, Fig. 3, *K*). In a majority of cases, the nuclei are eccentrically located. Centrally located nuclei (Fig. 4, *A*) have been observed in some eccentric halos but, for the most part, when the halo is eccentric, the nucleus is likewise eccentric. Occasionally, the nucleus is not located within a well-defined halo but is found in another part of the cytoplasm (Fig. 3, *F*, *G*, and *H*). The lightest part of the halo does not always surround the nucleus, as is often supposed. The nucleus inside the halo sometimes has a covering which is probably composed of a granulated dark cytoplasm or membrane part which has an irregular shape (Fig. 1, *C* and *F*, Fig. 2, *D*, Fig. 3, *E*, and Fig. 5, *G* and *K*).

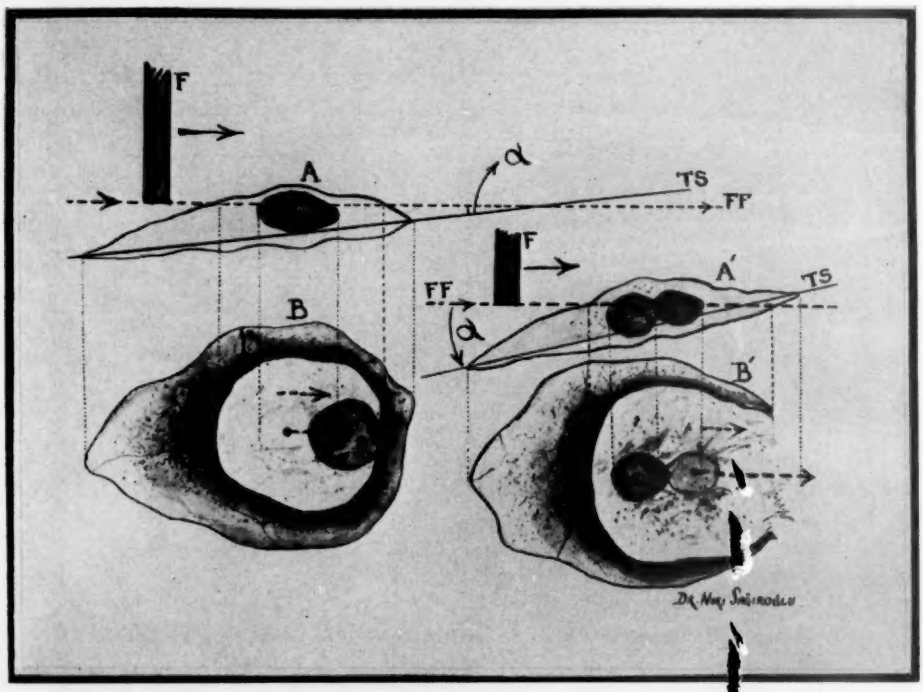

Fig. 9.—Mechanism of production of eccentric halo and nucleus.

A, *A'*, Side view of two cells in suitable condition from stratified squamous epithelium of uterine cervix.

B, *B'*, Top view of same cells.

TS, Transverse sectional surface of the cells which are parallel to the cervical surface.

F, Factor or scraper on cervical surface.

FF, Direction of the factor which is not parallel to transverse sectional surface on the cell.

α, Angles between *TS* and *FF*.

In Fig. 9, *B*, the nucleus is pushed away from its normal place and replaced eccentrically by factor in the same direction. In Fig. 9, *B'*, one of the nuclei is pushed out of the cell with one part of peripheral section of the cell. Compare with Fig. 5, *C*, and Fig. 6, *B*.

Sometimes the halo shows no nucleus inside, but outside, and just touching the border of the halo (Fig. 5, *C* and *F*), indicating that this nucleus belongs to this cell.

At times, leukocytes or erythrocytes are found inside the halo at the same level as the nucleus, and sometimes another small but complete cell is found within the halo (Fig. 1, *C* and *F*, Fig. 2, *H*, Fig. 3, *C*, *D*, *E*, *F*, and *G*, and Fig. 6, *B*). A cell that has a well-developed halo but no nucleus has also been observed (Fig. 1, *K*, Fig. 2, *H*, and Fig. 4, *B*, *C*, *D*, *E*, *F*, *G*, *H*, and *K*).

In some halos the nuclei are so small and pyknotic that one can easily decide the cell is normal or only slightly inflammatory (Fig. 1, *B*, *D*, *G*, and *K*, arrow).

Pathological Findings.—In the Cancer Institute at Miami, no biopsy method for diagnosis is used. For this reason, the pathological slides were taken from different sources for the histopathological studies of perinuclear halos.

Hundreds of histological slides from stratified squamous epithelium in normal, inflammatory, and neoplastic conditions have been studied. In all slides, the stratified epithelium has shown many halos. In cases of chronic nonspecific cervicitis the stratified squamous epithelium of the uterine cervix was covered with cells showing halos in histological slides (Fig. 10). These halos usually do not display an indented irregularity. Only in the side views of squamous cells do the halos have a fusiform shape with two sharp corners (Fig. 10, *A*, top).

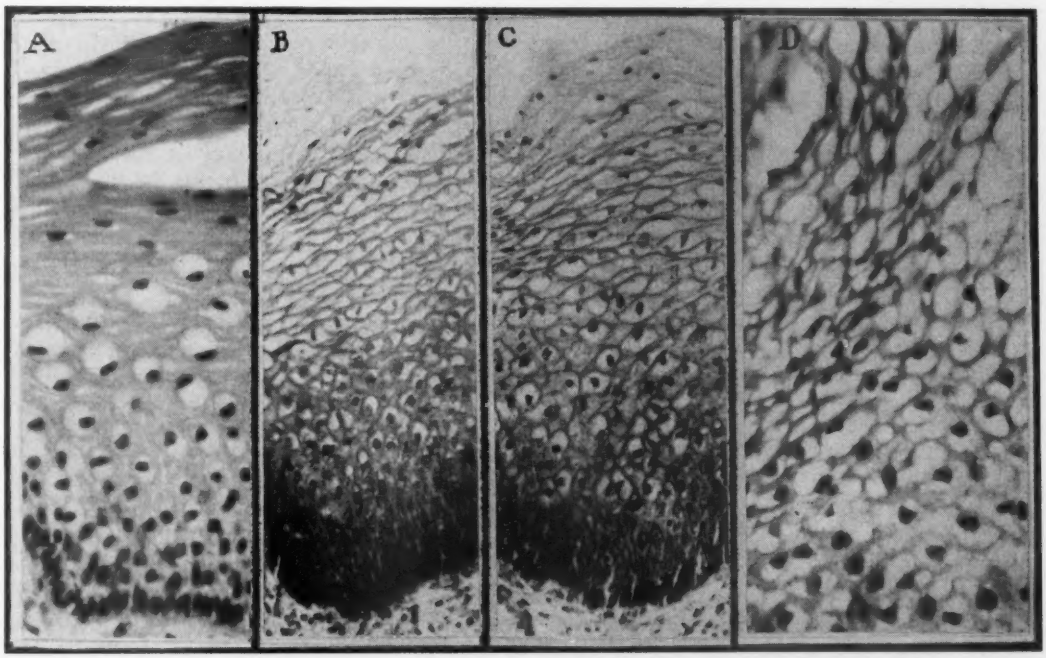

Fig. 10.—Histopathological photomicrographs of stratified squamous epithelium.

A, Cross section of the tissue showing defective cells or halos in intermediate levels; superficial cells do not show large defects because side views are presented.

B, *C*, and *D*, Semi-cross sections of the tissue showing defective cells or halos at all epithelial levels.

In many instances, the cell is made up entirely of a halo and a nucleus. with the exception of a tiny cellular border line, there is no separate cytoplasmic part of the cell. In eccentric halos the nuclei are usually eccentric. Some halos show no nuclei, as was found in the cytological area of study.

Comment

The development of the new TMK-101 staining technique proved to be a useful adjunct to the many other tools so vital to the progress of these studies.

With this method, there is no preliminary fixation, there is no contact with alcohol, ether, heat, or any other dehydrating agent. The fresh smear, made with the spatula, is placed immediately in the staining jar. In a matter of only 15 minutes, the cells assume a multicoloration similar to the results obtained when Papanicolaou's[7] technique is used. The mounting medium is the same TMK-101 dye solution. The cells retain their size and volume. The walls and the outlines, as well as the internal morphological construction of the halos, can be studied with ease.

In the Papanicolaou staining technique, it is not difficult to accept that a great part of the fine detail of the cytoplasm is destroyed under the dehydration series. Cells stained by Papanicolaou's method often have lost volume, become shrunken, and their upper and lower faces glued. Indeed, they have become stained "cell skeletons." Thus, the staining technique that is so perfect for cytodiagnostic work becomes one of the worst handicaps to the investigator engaged in human cell research.

The TMK-101 staining technique, therefore, has played a major role in this study of perinuclear halos. Clinically, cytologically, and pathologically, my findings support the hypothesis that the perinuclear halos seen in the precancer cell complex are the result of artifacts. In other words, the halos described and illustrated in this report are not inner halos; they appear to be the defects of cellular membranes and cytoplasm or superficial cavitations which occur under suitable conditions on some cells.

The Origin and Causes of Halos.—

Suitable conditions of the uterine cervix must be present and some external factors are involved in the production of halos. Suitable conditions may be said to occur when hyperactive, macerated, edematous, or easily friable cells are present on the surface of the cervix, such as are found in chronic nonspecific cervicitis. Under such conditions, the membrane and cytoplasm of some cells are partially lost. This is why leukocytes, erythrocytes, and occasionally a small cell can be seen inside some halos. These foreign bodies enter the primary cell through the previously referred to "lid" which they use as a kind of doorway opening into the cellular membrane. In rare instances, the cell nucleus is completely lost, leaving in a like manner.

Histological Findings of Chronic Nonspecific Cervicitis.—The stratified squamous epithelium is, as a rule, much thicker than normal. The superficial cells show irregular shapes and sizes. There are many deep-layer cells on the surface. The superficial cells are hyperactive, with an increase in material and fluid. The cytoplasm is thicker and more swollen or edematous. The cellular membrane is probably much thicker than normal. Scientists offer as the most reasonable cause of this condition a stasis in local blood circulation.

In an examination of the stroma surrounding the endocervical glands and underlying the squamous epithelium, it can be seen that, in the waning or healing stage of the chronic inflammation, collagen fibers laid down in the stroma undergo shrinkage and fibrosis with impairment of circulation. The squamous epithelium of the cervix may be 15 to 30 cell layers thick, yet have no blood vessels of its own.[4]

The fibrosis under the epithelial layer has strangled the veins more than the arteries. The blood cannot easily return, and stasis begins. The tissue and cells show edema. Clinically, a discharge begins. The nourishment of the epithelial layer is accomplished only by osmosis and diffusion. Therefore, the superficial cells cannot be sufficiently nourished. For this reason, some of the cells will die and develop maceration and, later, necrosis. This type of dead cell, found at the beginning of maceration, will show a microscopically higher top than the normal cell, especially the upper portion of the nucleus. If the surface of the cervix is studied as a surface only and is sufficiently enlarged,

it is possible to see that it is composed of hundreds of thousands of flat cones. Each cone is one squamous cell. Under the top of each cone, the nucleus is located (Fig. 7).

In normal or acute inflammatory cases, superficial cells are extremely flat and healthy (cornified cells). Of approximately the same height, the external factor (*F*) cannot perform a destructive act upon the membrane but in stages of chronic inflammation and in some other instances accompanying local maceration and necrosis, the top of the cell membrane is easily lost—somewhat similarly to that of a skin blister—under external disturbance. Around the cellular cone, the major part of the peripheral membrane is covered by other cells. Thus, the defect cannot extend to the edge of the cells. Each superficial cell, however, also has a free circumference on its peripheral part which covers the other cell. In this position, macerated cells can show an eccentric defect reaching to the edge of the cells (Fig. 9).

In cases labeled precancerous, the superficial cells have shown more hyperactivity and atypia than regular inflammatory cells. In addition to this, precancer cell complex cases are classified by pathologists as chronic nonspecific inflammations.

Papanicolaou[7] shows that chronic inflammation of the uterine cervix is probably the most common cause of atypical cytology. Selye,[11] in his original studies on the biological stress mechanism, shows a parallel between chronic inflammation and hypertrophia and hyperplasia. There is agreement, therefore, between leading cytologists and pathologists to the effect that there is a close relationship between chronic inflammation and atypical hyperactivity, or the precancer cell complex.

If an investigator is in all cases unable to observe halos or defects such as those shown in the photomicrographs and drawings (Figs. 1 through 9), the explanation is simply that there are no macerated cells on the surface or that the disturbing factors are lacking. Characteristic halos are usually present in the precancer cell complex, however, since this complex is most often the result of chronic inflammation. In addition, the cellular activity is stronger and the epithelial layers are thicker in precancerous cases than in chronic inflammation. Under these conditions, the macerated cells may be more common and the disturbing factors may influence more cells that are in suitable condition for pruning of their conical tops. Examples of microscopic craters or defects can be seen in the top view of cells in Fig. 5, *A* and *E*, and Fig. 6, as perinuclear halos.

Factors Influencing Production of Halos.—

1. The Spatula.—The Ayre wooden spatula, according to reasonable evidence, is the No. 1 producer of defects. It is true, however, that the Ayre spatula is the best tool for collecting the right cells from the uterine cervix for cytological examination. It is equally true that the spatula can easily tear away the top of macerated cell cones which are sharply exposed on the surface of the cervix. The Ayre spatula, although specifically designed for scraping the cervix and shaped in a manner which exactly fits the cervical surface, has sharp corners. Also, the spatula must be applied while dry. Thus, when it is turned on the cervix, even though the pressure is slight, the spatula scrapes, scratches, and uproots cells from the surface. It is therefore apparent that on some cells in suitable condition this technique will effect tearing-away, or shaving, or pruning of a part of the cellular membrane (Fig. 8).

The spatula can produce a secondary cellular defect when the material collected is smeared on a dry glass slide, by pushing or pulling.

Further evidence corroborating the negative aspects of Ayre's spatula: This particular kind of halo was first shown by Ayre, who created and used the spatula, in his studies of the precancer cell complex.

In collecting material for smears, it has been my experience that a much higher incidence of halos is evident when the spatula is used than when the pipette is used. In addition, smears made from second or third successive scrapings by spatula are seen to have approximately 10 times as many halos as smears made from initial scrapings.

2. The Speculum.—The round end of the vaginal speculum can scrape the cervix on insertion into the vagina and thus produce fewer defective cells than the spatula.

3. The Vaginal Examination.—Massage with the fingers on the cervix may produce some defects on macerated cells.

4. The Pipette, Vaginal Suppositories, Tampons, Douches, Etc.—One or all of these may be responsible for the mechanical production of halos.

5. Exfoliation.—While macerated cells are exfoliating, they may leave the membrane part of the underside adhering to the second cellular layer of the cervix or the superficial cell which is sometimes attached to a macerated cell, tearing away the front surface of the cells. This latter effect is found only rarely, however.

6. Delivery.—The head of the baby is the strongest scraper of the cervix when it is emerging. Halos, thus produced, can be seen from 1 to 15 days after delivery.

The Influence of Dyes on Cells With Halos.—

The homogeneous color observed microscopically in the cellular membrane of stained cells is due to the marked affinity of this part of the cytoplasm for the dye. In other words, the dye concentrates in this area. The chromatin content adds a slight granular appearance to the cytoplasm (Fig. 4, *A* and *B*).

It has been my experience that, if the halo were not a membrane defect, the stained membrane would cover the metabolic halo and we would see it only with great difficulty. Since the nucleus is the center of cellular metabolism, if the halo were a metabolic product, the lightest part would be placed around the nucleus, and it would darken progressively with the most intense coloration to be found in the outermost rim. How, then, can we explain that in some cells the halo is brightly lighted at its peripheral part and darker around the nucleus (Fig. 1, *E* and *F*, Fig. 2, *D*, Fig. 3, *E*, *F*, *G*, and *H*, and Fig. 5, *G* and *K*)? And, if the halos are not a torn edge, how can we explain the sharp, sometimes indented borders and the dark-stained edge that is folded over? In Fig. 2, *C*, *E*, *F*, and *K*, Fig. 3, *A*, *B*, *G*, *H*, and *K*, Fig. 4, *F*, Fig. 5, *B*, and Fig. 6, *B* it is clearly evident that the halos are torn membranes. If this were not true, we would not be able to see such sharp differences between the halo and the other cytoplasm.

Many cytologists have attempted to show that halos are the product of a changed cellular metabolism and a number of chemists are also working on this theory. Koss and Durfee[6] have carefully studied and meticulously examined eccentric halos and the nuclei contained therein, both cytologically and pathologically, and they report, "The significance of the perinuclear zones is not clear at this point. It is possible that the zones result from altered cellular metabolism."

In comparison, the halos shown in Fig. 6 are membrane defects. There is no membrane cover on the nuclei; they are attached to the halo only by cytoplasmic filaments.

In cases showing cells with halos, there is, as a rule, a thick leukocyte infiltration. Actually, in a majority of such cases, the cells are covered with leukocytes. Many halos may be found with one or more leukocytes within the halo (Fig. 1, *C* and *F*, Fig. 2, *H*, and Fig. 3, *C*, *E*, *F*, and *G*).

It will be seen, then, that halos usually appear on dead cells; that they are, in fact, a degenerative phenomenon.

Despite some opinions to the contrary, the top view of the halo is the same as the side-view picture. The naked cytoplasm and nucleus, as seen within the halo (top view), are similar to the appearance of a lighted open window in a darkened building. I believe that one who works or studies the cells with micromanipulator-attached microscope can easily remove the nucleus from the halo.

Therefore, it is postulated that the halos under discussion are artificially induced defects on cellular membranes and seemingly display no relation to the metabolism of dead cells.

The Production of Eccentric Halos and Nuclei.—

In eccentric halos and nuclei, the effective line of the external factor is not parallel to the cell surface. There is a narrow angle between them (Fig. 9). Thus, the membrane part is eccentrically torn away and the nucleus is pushed to the edge or the outside of both the halo and the cell. It seems evident that some naked nuclei observed in smears from precancer cell complex cases are probably the result of this phenomenon. If the disturbing factor *(F)* slightly touches the surface of the cell, the defect will belong only to the surface membrane—this may be termed "shaved"—and the halo in this case will be a shade lighter than the peripheral cytoplasm. In other cases, the factor cuts far into the cell, producing deep defects which, after staining, will be seen as lightly colored craters.

Interpretation of Pathological Findings.—

Koss and Durfee,[6] in cases which show halos in cytological and pathological slides by photomicrographs, seem convinced that they are confirming a truth: "These individual cells composing the focus were comparable with the abnormal cells seen in smears, and obviously were not the result of an artifact."

In the histopathological slides studied by these investigators, cell sections were observed; that is, the "defected" cells and not the complete cells seen in cytological smears were examined. In histopathological slides, if the section is tiny enough, all the cells have membrane and cytoplasmic defects. The blade of the microtome has usually cut the cells on both sides, especially in hyperactive anaplastic tissues. Cytological cells cannot be compared with histological cells in this respect. In pathology, the tissue is desirable if the section shows epithelial, subepithelial, and muscular or similar deep layers, for study. Therefore, the tissue must be cross-sectioned. Because the side view is presented in cross sections, the blade is not parallel to the large surface of the cell and the halos or defects are indistinct in superficial squamous cells. Thus, the resulting halos have a fusiform shape. The intermediate cells have a larger volume in their side view, as in their top view, and the halos are clearly visible (Fig. 10, *A*).

Histopathological slides, however, are not always presented in cross section. It is frequently difficult to place in cross position, under a microtome, the tissue which is irregularly pressed into a paraffin block. Thus, pathological sections usually are semi-cross sections (Fig. 10, *B*, *C*, and *D*), and many halos in all types of diseases of the stratified squamous epithelium are easily seen as well as in normal tissue.

Histopathological halos usually do not have clear, dark outlines because the blade of the microtome is extremely sharp. It has "shaved" the cells but does not tear away material as does the spatula. Some cells in histological slides do not show halos because: (1) the nucleus is very large, occupying all of the cellular space, as in the case of basal cells; or (2) the blade cannot cut the membrane while the cell is very thin, or the section thicker than the cell, especially in an exact cross section of normal tissue.

If the section were parallel to the surface of the tissue, all the cells would show large defects. In all histological sections of stratified squamous epithelium, the halos under discussion were seen, but only 33 of 109 cytological cases, specifically selected, showed halos. This is a significant finding.

In the Live Cell Experimental Laboratory of the Cancer Institute at Miami, many anaplastic or inflammatory tissue cultures from the cervical epithelium were examined; the halos under discussion were not observed.

Finally, the halos which were found by Koss and Durfee in pathological sections have not proved their theory, but substantiate the theory that the *halos under discussion are the result of artifacts as membranous and cytoplasmic defects.*

Summary and Conclusion

1. One hundred and nine research patients were clinically and cytologically studied by cervical scraping smears from December, 1956, to February, 1958, in the Cancer Institute at Miami, Florida. These cases were cytologically diagnosed as inflammatory or precancer cell complex.

2. The cells from 33 of the cases have displayed halos covering a large area, and showing sharp and dark border lines.

3. The clinical, cytological, and pathological evidence gained from these cases seems to prove that the halos observed are, in fact, not perinuclear halos but are membrane and cytoplasm defects on the surface of the cells, induced generally by mechanical factors, under suitable conditions of the uterine cervix.

4. In practical cytology, these halos have been shown as important evidence of the existence of the precancer cell complex. It is evident from results presented and discussed that halos or membrane defects have resulted from dead and macerated cells.

5. From a diagnostic viewpoint, there is inflammatory hyperactivity in cells with multinucleation. If halos accompany this condition, the cytologist may automatically diagnose the case as "precancer." If one considers that the naked nuclei which can be freed from the halos are characteristic of maximal anaplastic changes of the precancer cell complex, the biopsy in such cases may not confirm the cytological diagnosis. Thus, the cytologist must be extremely careful in examining the slides with defective cells and naked nuclei in the precancer cell complex.

I wish to acknowledge the great interest of J. Ernest Ayre, the Director of the Cancer Institute at Miami, Cancer Research and Cytology Center, where this work was performed; also the assistance of Miss M. D. Bellomy in the preparation of this manuscript.

References

1. Ayre, J. E.: Ann. New York Acad. Sc. **63**: 1263, 1956.
2. Ayre, J. E.: Am. J. Obst. & Gynec. **58**: 1205, 1949.
3. Ayre, J. E.: Acta cytologica **1**: 50, 1957.
4. Ayre, J. E.: Congrés internat. de gynécologie et obstétrique, Geneva, 1954, Georg & Cie, p. 103.
5. Herbut, P. A.: Gynecological and Obstetrical Pathology, Philadelphia, 1953, Lea & Febiger, p. 195.
6. Koss, L. G., and Durfee, G. R.: Ann. New York Acad. Sc. **63**: 1245, 1956.
7. Papanicolaou, G. N.: Atlas of Exfoliative Cytology, Cambridge, 1954, Harvard University Press, pp. 27-132.
8. Papanicolaou, G. N.: Science **95**: 438, 1942.
9. Sağiroğlu, N.: A New Rapid Multicolor Staining Technique in Medical Cytology for Office Practice. (To be Published.)
10. Sağiroğlu, N.: Cancer Cytology **1**: 10, 1958.
11. Selye, H.: The Story of the Adaptation Syndrome, Montreal, 1952, Acta, Inc.

CYTOLOGY: AN EVALUATION AND FOLLOW-UP OF 25,000 GENITAL SMEARS*

WM. J. ESTRADA, M.D., S. J. SKINNER, M.D., GEORGE V. MILLER, M.D., AND A. M. FARIS, M.D., HOUSTON, TEXAS

(From the Departments of Gynecology and Pathology, Hermann Hospital)

THIS paper presents an evaluation of the results obtained by the use of cytology in the detection of cervical malignancy by physicians engaged in varied fields of medicine, submitted to a single group of pathologists, and also a critical evaluation of the follow-up of positive and suspicious smears. In this analysis of smears, both premalignant and borderline lesions, i.e., carcinoma in situ and severe atypical epithelial hyperplasia of the cervix, have been included under malignancies of the cervix.

Material

The work reported covers the period from Jan. 1, 1952, through Sept. 15, 1957. During this time, 25,000 consecutive smears from 17,000 women in the Houston area were studied. Smears taken from patients as a part of the follow-up for treated carcinoma of the cervix and smears with unsatisfactory preparations were excluded from the study. All of the smears were reviewed by the pathologist. The smears were fixed and stained according to the Papanicolaou technique and were grouped according to Papanicolaou's classification.[9, 10, 12]

Sites of Collection.—As shown by Table I, the smears were obtained from several locations, but principally from the cervix. Of the entire series, 60.04 per cent were cervical in origin and yielded 77.1 per cent of the suspicious or positive smears, while 32.16 per cent were vaginal in origin, but yielded only 19.08 per cent of the suspicious or positive smears.

TABLE I. SOURCE OF MATERIAL AS TO SITE OF ORIGIN

LOCATION	TOTAL	% OF TOTAL SMEARS	% OF SUSPICIOUS OR POSITIVE SMEARS
Vaginal	8,040	32.16	19.08
Cervical	15,010	60.04	77.1
Cervical and vaginal	1,655	6.62	2.29
Endometrial alone or with cervical	295	1.18	1.53
Total	25,000	100.00	100.00

The cervix is the preferred site of collection of routine smears with the Ayre spatula[1] or a similar instrument to scrape gently the squamocolumnar junction. It is the impression of the pathologists that this site yields a greater

*Presented at a meeting of the Texas Association of Obstetricians and Gynecologists, Feb. 15, 1958.

concentration of malignant cells and a better-quality smear without cellular distortion. An endometrial aspiration smear is more reliable than a cervical or vaginal smear in screening for endometrial carcinoma.

Analysis of Smears

Cytological Analysis Reports.—As shown by Table II, 1.05 per cent or one out of every 95 smears, was classified as suspicious or positive. There were 4 Class I smears for every Class II smear in the series.

TABLE II. CYTOLOGICAL ANALYSIS REPORT

CLASS	NO. SMEARS	%	
Negative.—			
Class I	19,928	79.711	
Class II	4,810	19.25	
Suspicious.—			
Class III	175	0.700	1.05%
Positive.—			
Class IV	76	0.304	
Class V	11	0.045	

Histological Diagnosis, Correlation of Smear With Biopsy Results.—Table III shows the suspicious and positive smears of which a neoplastic lesion was found as the source.

TABLE III. HISTOLOGICAL DIAGNOSIS. CORRELATION OF POSITIVE SMEAR WITH POSITIVE BIOPSY RESULTS

CLASS	NO. CASES	LESIONS OF CERVIX				CARCINOMA OF ENDOMETRIUM	CARCINOMA OF		
		INVASIVE SQUAMOUS-CELL CARCINOMA	CARCINOMA IN SITU	ATYPICAL EPITHELIAL HYPERPLASIA	ADENOCARCINOMA		TUBE	OVARY	BLADDER
III	128	34	56	25		12*	1		
IV	73	34	32	2	1	2		1	1
V	11	8	3						
Total	212	76	91	27	1	14	1	1	1

*Includes 2 cases of severe atypical endometrial hyperplasia bordering on carcinoma.

There were 212 Class III, IV, and V smears associated with borderline, premalignant, and malignant lesions. This figure included: 76 cases of invasive squamous-cell carcinoma of the cervix, one case of adenocarcinoma of the cervix, 91 cases of carcinoma in situ of the cervix, 27 cases of atypical epithelial hyperplasia of the cervix, 14 cases of endometrial carcinoma (including 2 cases of severe atypical endometrial hyperplasia bordering on carcinoma), and 3 malignancies elsewhere in the genital tract. One neoplastic lesion of the bladder was also detected by the genital smear.

From the figures presented, we find that: (a) for every 95 smears submitted there was one positive or suspicious smear; (b) for every 128 smears submitted there was one preinvasive or invasive lesion of the cervix; and (c) for every 118 smears submitted there was one premalignant or malignant lesion of the genital tract.

There were 148 unsuspected neoplasms of the cervix, the smears from which constituted 65 per cent of the 212 suspicious or positive smears with a positive

biopsy for malignancy. Over 60 of these patients were recorded as having an essentially normal-appearing cervix. Eight of these normal-appearing cervices were found to harbor an invasive squamous-cell carcinoma.

False Negative Smears.—Smears which were reported as showing no evidence of malignancy from patients who were found on subsequent biopsy to have a neoplastic lesion were classified as false negatives. The number of false negatives is obviously very difficult to assess accurately, since it is evident that, in asymptomatic patients, further diagnostic procedures were not performed when the smear was reported as negative. Graham and Meigs[4, 5] stated the false negative percentage in known series, i.e., smears taken from known preinvasive and invasive carcinoma, to be 10 per cent. Cuyler and his group[3] have found similar results.

In this series, there were 4 false negative smears: 2 were Class I, 2 were Class II, and all 4 revealed carcinoma in situ on subsequent histological examination.

Twenty-one cases of endometrial carcinoma were found in this series. Seven of these, or 33.3 per cent, had negative smears; this compares favorably with results from other series of cervical smears in the detection of endometrial carcinoma.[6, 13] Of the 21 cases of endometrial carcinoma only 4 were studied by endometrial aspiration smear,[11] and all of these were positive.

Women with postmenopausal bleeding, in whom endometrial carcinoma is suspected, can be studied to better advantage by curettage and histopathological examination than by cervical or endometrial smears.

False Positive Smears.—False positive smears are defined as smears classified as Class III, IV, or V, taken from patients upon whom subsequent adequate follow-up revealed no malignant or premalignant lesion.

There were 12 cases classified as false positive. Twenty-three additional cases with Class III or IV smears showed no evidence of a neoplastic lesion after inadequate follow-up procedures, but we do not feel that these can be called definite false positives. Any follow-up which falls short of a cold knife conization of the cervix and fractional curettage of the uterus will not suffice to eliminate the possibility of a neoplastic lesion giving rise to a Class III, IV, or V smear. In this series, we have included these in our false positive group, since some tissue was available for study.

A total of 33 Class III and 2 Class IV smears made up the false positive group. From Table IV, the 33 Class III smears represented on histological examination of tissue, 14 cases of chronic cervicitis and 19 cases of squamous metaplasia. The Class IV smears were from one case of chronic cervicitis and one case of squamous metaplasia. Seven of this total also showed atrophic changes, and 2 were from recent abortions.

TABLE IV. PATHOLOGICAL DIAGNOSES FROM 35 FALSE POSITIVE SMEARS

CLASS	NO. CASES	CHRONIC CERVICITIS	SQUAMOUS METAPLASIA (EPIDERMIZATION)
III	33	14	19
IV	2	1	1

False positives constituted 0.14 per cent of the total series and 13.3 per cent of the total number of Class III, IV, and V smears. False positive smears are generally found in cases with severe inflammatory processes, or in epithelial regeneration, hyperplasia, or metaplasia as detailed in Table IV.

It is known that upon occasion a small cervical carcinoma will give rise to a positive smear and that the lesion may be missed on subsequent punch biopsy of

the cervix. Cuyler[3] reported that 5 patients, whose smears were classified initially as false positive, later were found to have 3 intraepithelial carcinomas and 2 invasive squamous-cell carcinomas.

The so-called false positive cases, despite the negative initial biopsies, demand a careful follow-up. The smear, although less conclusive, has an advantage over the punch biopsy in that it provides a sampling of the whole epithelial lining; whereas, the biopsy encompasses a relatively small area.

Repeatedly positive smears, even in the face of a negative fractional curettage and cold cervical conization, should lead one to suspect a lesion elsewhere in the genital tract.

TABLE V. FOLLOW-UP STUDIES OF THE 12 FALSE POSITIVE SMEARS, INCLUDING THE INADEQUATE FOLLOW-UP OF 23 CLASS III AND IV SMEARS

Biopsy of cervix alone	7	
Biopsy of cervix and endometrium	5	
Biopsy of cervix and endometrium with negative follow-up smears	11	
		23 with insufficient follow-up
Fractional curettage and cold knife conization of cervix	6	
Fractional curettage and cold knife conization of cervix with negative follow-up smears	6	
		12
Total		35

As shown in Table V, of the 35 cases reported as false positive, 23 received inadequate follow-up, in that a fractional curettage and cold knife conization were not done. In 7 cases a biopsy only of the cervix was performed; in 5 a biopsy only of the cervix and endometrium; in 11 cases a cervical and endometrial biopsy only, but these did have negative follow-up smears. The remaining 12 smears were properly followed. Therefore, of the total of 35 false positive smears, 23 (65.7 per cent) were improperly followed.

Smears With No Histological Follow-Up.—There were 15 cases of suspicious or positive smears in which no tissue was available for histological study. Of these, there were 14 Class III and one Class IV smear.

Analysis of this group shows that 7 patients refused biopsy, 3 patients could not be located, one patient continues to have a suspicious smear, but the physician has failed to do a biopsy. One patient had a total hysterectomy in 1947 for myomas and now has a Class III smear of the vaginal cuff, treated by silver nitrate cauterization. In another case cauterization was done at the time the smear was taken, and follow-up fractional curettage and cold knife conization revealed only severe heat cautery effect. Finally, 2 patients were treated with suppositories and douches, and repeat smear elsewhere was reported as negative.

As with the false positive group and now with this unknown follow-up group, the smear is worthless without adequate histological follow-up. It is felt that little can be done by the physician with patients who refuse to return for biopsy. However, the physician should pursue vigorously all the patients with Class III, IV, or V smears and should see that none escapes follow-up because of any failure or procrastination on his part.

Analysis of the Follow-Up on Positive and Suspicious Smears.—The majority of smears were followed as is advocated, with or without biopsy first, and then by a fractional curettage and cold knife conization. The complete follow-up was not available in all cases, but from our records there were 50 cases, or 19 per cent, felt to have had an improper follow-up (Table VI).

The value of proper follow-up can be illustrated by the following cases taken from this series. There were 4 cases of carcinoma in situ, one of atypical hyperplasia, and one of chronic inflammation of the cervix on biopsy, all of which proved to be invasive carcinoma of the cervix on cold knife conization. There were 3 cases of atypical epithelial hyperplasia of the cervix by biopsy, which on conization revealed carcinoma in situ. There was one case of chronic cervicitis by biopsy, which on conization revealed atypical epithelial hyperplasia.

TABLE VI. THE 50 CASES IMPROPERLY FOLLOWED

Biopsy alone (11 are now being followed by routine cervical smear)	23
Unknown, excluding the 7 cases in which the patient refused to return	8
Carcinoma in situ of the cervix on biopsy followed by total hysterectomy	9
Handled elsewhere and by physicians other than the one who had submitted the smear. One treated by radium and the other by total hysterectomy. The diagnosis in both was carcinoma in situ of the cervix	2
Cases of atypical epithelial hyperplasia of the cervix with biopsy only	6
Total hysterectomy without cone after a biopsy had revealed atypical epithelial hyperplasia of the cervix	2
Total	50

Malignancies Elsewhere in the Genital Tract.—Many reports have been written on the findings of malignancies elsewhere in the genital tract with the use of vaginal or cervical smears.[7, 14, 15] Most of these are concerned with either carcinoma of the Fallopian tube or of the ovary. In this series, we found 3 such instances. There was one case of carcinoma of the ovary, one case of carcinoma of the Fallopian tube, and one case of metastatic carcinoma from the bladder.

Cytological Studies of Pregnant Patients.—There were only 250 smears known to have been submitted from pregnant or postpartal women. Of the 250 smears submitted, there were 5 Class III or IV smears. Of these 2 were false positive, 2 showed carcinoma in situ of the cervix, and one showed invasive squamous-cell carcinoma of the cervix.

Pregnancy does not interfere with the reading of Papanicolaou smears, but interpretation is more difficult because of cellular changes which regress after delivery. The smear has a definite advantage over biopsy in pregnancy, in that the pregnant cervix is extremely vascular and biopsy may be followed by excessive bleeding.

In this group, there was a proved premalignant or malignant lesion of the cervix for one out of every 82 smears compared to one out of every 128 smears in the entire series. Although this number is small for comparison, it does show a need for more extensive use of the smear in screening the pregnant patient for cancer of the cervix.

Who Should Be Routinely Studied?—The largest number of smears in this series was taken in the age group between 30 and 50 years, accounting for 15,243, or 61 per cent of the total smears. In the age group below 30 years, 4,066 smears or 16.2 per cent were taken.

The average age of patients with invasive squamous cell carcinoma of the cervix was 50.5 years, of those with carcinoma in situ of the cervix 37.5 years, and of those with atypical epithelial hyperplasia of the cervix 36.5 years.

In the age group below 30 years, there were 26 Class III smears and 6 Class IV smears. The histological studies showed 4 cases of invasive squamous-cell carcinoma of the cervix, 16 cases of carcinoma in situ of the cervix, and 8 cases of atypical epithelial hyperplasia of the cervix. Three cases were found to be false positive, and one is unknown.

TABLE VII. CORRELATION OF CYTOLOGICAL CLASSIFICATION AND HISTOLOGICAL DIAGNOSIS WITH AGE OF PATIENT

HISTOPATHOLOGICAL DIAGNOSIS	CLASS			AGE IN YEARS									
	III	IV	V	15-20	20-30	30-40	40-50	50-60	60-70	70-80	OVER 80	UNKNOWN	TOTAL
Carcinoma in situ	56	32	3	2	14	38	27	6	2	1		1	91
Atypical hyperplasia of cervix	25	2	0		8	12	3	2	1	1			27
Invasive carcinoma of cervix	34	34	8		4	16	19	13	12	11		1	76
Endometrial carcinoma	12	2	0				7	2	5				14
Carcinoma of fallopian tube	1									1			1
Carcinoma of ovary		1					1						1
Carcinoma of bladder		1							1				1
Adenoma carcinoma of cervix		1				1							1
Total	128	73	11	2	26	67	57	23	21	14	0	2	212
Unknown	14	1			1	3	5	3	2			1	
Chronic cervicitis or metaplasia	33	2			3	10	6	6	4	1	2	3	

Carcinoma of the cervix is rarely encountered in women under 20 years, but invasive carcinoma of the cervix is by no means uncommon in the 20 to 30 year age group. Borderline carcinoma is common between the ages of 20 and 30 years. We, then, recommend routine cytology studies on all women over 20 years of age. Table VII gives a correlation of cytological classification and histological diagnosis with the age of the patient.

Routine Smears on a Regular Follow-Up Basis.—In this series, 17 of the patients with positive or suspicious smears had had previous negative smears. The interval varied from 8 months to 3 years. The histological diagnoses in these cases were: 10 cases of carcinoma in situ of the cervix; 3 cases of atypical epithelial hyperplasia of the cervix; 2 cases of endometrial carcinoma; and 2 unknown that could not be located.

Novak[8] believed that a routine pelvic examination should be done at least every 6 months. We concur with this statement, and add that a Papanicolaou smear should be a part of this examination.

Necessity of Correlation of Smear Findings With Histological Studies.—The Class III smears seemed to have caused little alarm on the part of some of the submitting physicians, although 128 out of the 175 Class III smears were indicative of a premalignant or malignant lesion. If the 14 unknown Class III smears are excluded, then 128 out of 161 Class III smears, or 79.5 per cent, revealed a neoplastic lesion.

A positive or suspicious smear should be regarded with respect and every effort made to establish the diagnosis before the patient is treated. A positive smear should never be considered as providing conclusive evidence of the disease; the final diagnosis rests upon microscopic examination of a sufficient amount of tissue. The investigation should continue until a satisfactory diagnosis can be made by the pathologist; and, if repeatedly positive smears are found, persistent efforts to establish a diagnosis must be made. Some feel that a persistently positive smear after negative curettage and conization of the cervix may be an indication for an extensive study, possibly a celiotomy,[7] in search of genital or even extragenital malignancies.

We believe that the best method of handling a patient with a positive or suspicious smear is to do an endometrial and cervical biopsy on an outpatient basis; if this is negative, then a fractional curettage of the uterus and cold knife conization of the cervix are done in the hospital. This provides adequate material for the diagnosis of malignancy of the cervix[2, 14] or endometrium. The use of the punch biopsy and endometrial biopsy prior to hospitalization may eliminate the need for a fractional curettage and conization, and thereby an anesthetic, if the biopsy establishes invasive carcinoma of the cervix.

The punch biopsy of the cervix missed 18.5 per cent of the lesions (early) in a series at Duke University,[3] leading to a grave, false sense of security. If adequate follow-up procedures are negative, the patient should continue to be followed with cervical smears.

Summary and Conclusions

1. A critical review of the results of 25,000 smears on 17,000 women by 82 physicians in varied fields of medicine is presented.

2. Of the total smears submitted, 1.05 per cent were positive and 0.85 per cent revealed a premalignant or malignant lesion.

3. A brief discussion of false positive and false negative smears is presented.

4. The cervical smear was felt to be superior to smears from other sites, but was not felt to be adequate for detection of endometrial carcinoma.

5. The average ages of patients with premalignant and malignant lesions of the cervix is given.

6. Cytological studies should be considered a routine part of obstetrical and gynecological office examinations, with smears being taken once a year on women under the age of 30 years and every 6 to 12 months thereafter. The value of the routine smear in the below 30 age group is emphasized.

7. The necessity for adoption of routine follow-up procedure of positive smears is emphasized. This is done by: (1) biopsy, and if necessary followed by (2) a fractional curettage and cold knife conization of the cervix. Fifty cases (19 per cent) in this series were improperly followed up.

8. The use of the cervical smear in the obstetrical patient is encouraged.

Addendum.—Since the completion of this paper, one of the patients in the unknown group has been found to have carcinoma in situ and one in the false positive group to have primary papillary carcinoma of the ovary.

References

1. Ayre, J. E.: Am. J. Obst. & Gynec. **53**: 609, 1947.
2. Carter, B., Cuyler, W. K., Kaufmann, L. A., Thomas, W. L., Creadick, R. N., Parker, R. T., Peete, C. H., Jr., and Cherny, W. B.: Am. J. Obst. & Gynec. **71**: 634, 1956.
3. Cuyler, W. K., Kaufmann, L. A., Carter, B., Ross, R. A., Thomas, W. L., and Palumbo, L.: Am. J. Obst. & Gynec. **62**: 262, 1951.
4. Graham, R. M., and Meigs, J. V.: Am. J. Obst. & Gynec. **58**: 843, 1949.
5. Graham, R. M.: in Meigs, J. V., and Sturgis, S. H., editors: Progress in Gynecology, New York, 1950, Grune & Stratton, vol. 2, pp. 133-138.
6. Hecht, E. L.: New York J. Med. **52**: 2745, 1952.
7. Larsson, E., and Schooley, J. L.: Am. J. Obst. & Gynec. **72**: 1364, 1956.
8. Novak, E.: Am. J. Obst. & Gynec. **58**: 851, 1949.
9. Papanicolaou, G. N.: Science **95**: 438, 1942.
10. Papanicolaou, G. N., and Traut, H. F.: Diagnosis of Uterine Cancer by the Vaginal Smear, New York, 1943, The Commonwealth Fund.
11. Papanicolaou, G. N., and Marchetti, A. A.: Am. J. Obst. & Gynec. **46**: 421, 1943.
12. Papanicolaou, G. N.: Atlas of Exfoliative Cytology, Cambridge, Mass., 1954, Harvard University Press, pp. 3-6.
13. Reagan, J. W., and Sommerville, R. L.: Am. J. Obst. & Gynec. **68**: 781, 1954.
14. Slate, T. A., Martin, P. L., and Merritt, J. W.: Am. J. Obst. & Gynec. **66**: 878, 1953.
15. Song, Y. S.: Am. J. Obst. & Gynec. **73**: 341, 1957.

PATIENT ACCEPTANCE AND COMPARATIVE VALUE OF THREE DIFFERENT METHODS OF OBTAINING VAGINAL SMEARS FOR THE DETECTION OF CARCINOMA OF THE CERVIX

WILLIAM POMERANCE, M.D., HARRY J. GREENE, M.D.,
HERBERT E. NIEBURGS, M.D., AND ABRAHAM OPPENHEIM, M.D.,
BROOKLYN, N. Y.

(From the Division of Cancer Control and Research of the New York City Department of Health and the Jewish Hospital of Brooklyn)

THIS project was begun as a pilot study to determine the acceptability of a self-obtained vaginal smear program in patients of a low socioeconomic stratum as well as a comparison of the value of two different self-obtained smears, namely, the applicator smear and the tampon smear. This program was applied to the clinic population of the Jewish Hospital of Brooklyn, which is situated on the fringe of a large area almost entirely composed of people in a rather low socioeconomic class and predominantly Negro. Very few of these people would ordinarily seek cancer screening. The applicator used has been presented previously and was suggested by Dr. Oppenheim of the Department of Health of New York City. The tampon, developed by Dr. Nieburgs, also has been presented before; it has a device which has been shown to secure the transfer of about 95 per cent of all cervical cellular material without the necessity of selecting any special area of the tampon.

Method of Study

The program was applied by first interviewing patients in the various clinic departments, obtaining a short history, and then giving each of these patients an applicator and a slide. She was then instructed in the method of using these and told to go to the bathroom and return with the prepared slide. On her return with the applicator smear, the patient was then given a packet containing a tampon, a detailed instruction sheet with diagram, and slides in a box. The nature of the tampon was explained orally and she was told to insert the tampon in 4 days and leave it in overnight, or for at least 6 hours, and to return to the clinic with the prepared slides 3 to 4 days after their preparation. She was given an appointment for this return visit, at which time the tampon slides were properly catalogued and the patient placed in lithotomy position and a cervical smear taken by a member of the gynecological house staff. All the smears were examined in Dr. Nieburgs' laboratory.

Patient Acceptability

All the patients, with only an extremely rare demurrer, complied with the initial aspects of the program and obtained an applicator smear. With

reference to the acceptance of the remainder of the program, it will be noted from Table I that 38 per cent complied fully and 4 per cent complied partially. It should be noted that partial compliance actually implies full compliance, since in many instances the incomplete compliance was due to the failure of a house staff officer to be available at the precise time the patient returned to the clinic. This then implies that 42 per cent of the patients accepted the program. The need to break this figure down seemed necessary, however, since 29 per cent of our patients were attending the prenatal clinic and in a sense, therefore, were to be considered almost a captive group. It should be noted, too, that there seemed to be no difference in the acceptance of any of the three methods; the patients accepted the tampon as readily as the smear taken by the physician even though only about 6 to 7 per cent ordinarily use tampons for menstrual hygiene.

In Table I it will be seen that 65 per cent of our pregnant patients completed our program, while almost exactly one half as many, or 33 per cent, of our nonpregnant patients complied. This last figure is a very discouraging one and is indicative of the fact, we believe, that only one out of every 3 patients in a low socioeconomic group, will avail herself of any screening program by appointment for a future date. It appears that the screening program must come to the patient wherever she is and avail itself of her presence by immediately subjecting her to the obtaining of a cytological spread.

TABLE I. DEGREE OF ACCEPTANCE OF SCREENING PROGRAM BY PREGNANT AND NONPREGNANT PATIENTS

TYPE OF PATIENT	NUMBER OF PATIENTS		NUMBER OF PATIENTS ACCEPTING PROGRAM							
			COMPLETE ACCEPTANCE (THREE SMEARS)		PARTIAL ACCEPTANCE (TWO SMEARS)		TOTAL		NONACCEPTANCE (ONE SMEAR)	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
Total	1,902	100	724	38	83	4	807	42	1,095	58
Pregnant	556	100	340	61	23	4	363	65	193	35
Nonpregnant	1,346	100	384	29	60	4	444	33	902	67

TABLE II. DEGREE OF ACCEPTANCE OF SCREENING PROGRAM BY ETHNIC GROUPS AMONG PREGNANT AND NONPREGNANT PATIENTS

ETHNIC GROUP	NUMBER OF PATIENTS		NUMBER OF PATIENTS ACCEPTING PROGRAM							
			COMPLETE ACCEPTANCE (THREE SMEARS)		PARTIAL ACCEPTANCE (TWO SMEARS)		TOTAL		NON-ACCEPTANCE (ONE SMEAR)	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
Pregnant.—										
White	93	100	45	48	5	5	50	54	43	46
Negro	438	100	284	65	17	4	301	69	137	31
Puerto Rican	25	100	11	44	1	4	12	48	13	52
Nonpregnant.—										
White	501	100	175	35	23	5	198	40	303	60
Negro	822	100	203	25	37	5	240	29	582	71
Puerto Rican	22	100	5	23	–		5	23	17	77
Unknown	1		1		–		1		–	

Analysis of our figures by race distribution does not seem to indicate any marked tendency to greater compliance by any one race (Table II). Analysis of our results by age distribution in the nonpregnant patients (Table III),

however, shows a very poor acceptance by the very young patients and a steadily increasing acceptance by those in each succeeding decade. This is demonstrated graphically in Fig. 1.

Comparison of Reliability of Smears Obtained by Three Different Methods

For purposes of comparison of the possible value of the various types of smears, we have used only the patients by whom there was complete compliance: i.e., all three smears had been obtained. We have considered these results according to the number present in each of the categories to which the cells on the slide were assigned, or the smear itself appraised. The categories decided upon at the outset of the study are listed in Table IV.

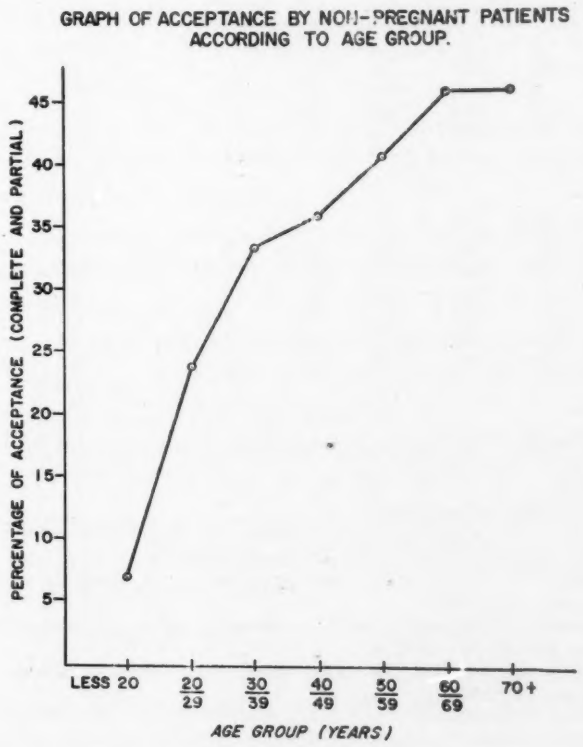

Fig. 1.

Table V presents a summary of these findings. If we were to consider categories 5, 6, 7, and 8 as one, it is to be noted that the percentage of positive and possibly positive smears was statistically greater for the physician smear than either the tampon or the applicator smear. If, however, we consider only the positive smears (categories 6 and 7), no such statistical superiority is evident. Furthermore, in these two categories we find 3 patients; the same patient found by all three smears was found to have carcinoma in situ of the cervix. The patient listed as positive for only the tampon smear and the patient listed as positive for only the physician smear were subsequently found to have no carcinoma; one had so-called squamous metaplasia, and the other had basal-cell hyperactivity. This gives a score of a false positive for both the tampon smear and the physician smear. We would like to note further that one patient listed as having an equivocal physician smear (category 8) was subsequently found to have carcinoma in situ. Thus far

none of the others have been found to have malignancy. We have not attempted to evaluate the absolute adequacy of each of these methods, since it is apparent that this would have to include a consideration of the number of false negatives in those found to have normal or benign abnormal cells. Such a study was not made, however.

TABLE III. DEGREE OF ACCEPTANCE OF SCREENING PROGRAM BY AGE GROUPS AMONG PREGNANT AND NONPREGNANT PATIENTS

AGE GROUPS	NUMBER OF PATIENTS		NUMBER OF PATIENTS ACCEPTING PROGRAM							
			COMPLETE ACCEPTANCE (THREE SMEARS)		PARTIAL ACCEPTANCE (TWO SMEARS)		TOTAL		NON-ACCEPTANCE (ONE SMEAR)	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
Pregnant.—										
Under 20 years	49	100	36	73	–		36	73	13	27
20-29 years	314	100	191	61	12	4	203	65	111	35
30-39 years	179	100	104	58	10	6	114	64	65	36
40-49 years	12	100	8	67	–		8	67	4	33
Age unknown	2		1		1		2		–	
Nonpregnant.—										
Under 20 years	30	100	2	7	–		2	7	28	93
20-29 years	347	100	74	21	9	3	83	24	264	76
30-39 years	414	100	115	28	21	5	136	33	278	67
40-49 years	243	100	70	29	18	7	88	36	155	64
50-59 years	164	100	64	39	4	2	68	41	96	59
60-69 years	109	100	44	40	6	6	50	46	59	54
70 years and over	37	100	15	41	2	5	17	46	20	54
Unknown	2		–		–		–		2	

TABLE IV. CODE USED IN DESCRIBING CELLS AND SMEARS

1. Negative
2. Slight nuclear enlargement
3. Moderate cellular changes in superficial and intermediate cells
4. Dyskaryosis in superficial and intermediate cells
5. Dyskaryosis in intermediate and parabasal cells, possibly associated with carcinoma in situ
6. Dyskaryosis in parabasal cells associated with carcinoma in situ. Invasion cannot be ruled out
7. Cellular changes apparently associated with invasive cancer
8. Equivocal. Describe
9. No endocervical cells
10. Insufficient cells
11. Smear improperly prepared

The next three categories, "no endocervical cells," "insufficient cells," and "improperly prepared cells," were included as a possible measure of the adequacy of the smear techniques. In the category of "no endocervical cells" there is a statistical superiority of the physician smear over both the applicator and the tampon smear. In the category of "insufficient cells" there is a statistical superiority of the physician-obtained smear over the applicator smear, but no such superiority over the tampon smear. In the category of "improperly prepared smear" the numbers are so small as to make comparison unwarranted.

Other considerations that must be included in a total evaluation are such matters as the unit cost in terms of time and money and the incidental benefits to be derived from a physician examination which can be made at the time of obtaining a physician smear. These aspects have not been evaluated thus far by us.

TABLE V. RESULTS OF CYTOLOGICAL EXAMINATION OF SMEARS OBTAINED BY THREE METHODS FROM EACH OF 724 WOMEN

METHOD	TOTAL	CLASSIFICATION										
		NO. 5	NOS. 6 AND 7	NO. 8	TOTAL POSITIVE AND POSSIBLY POSITIVE		NO ENDOCERV. CELLS		INSUFFICIENT CELLS		IMPROPERLY PREPARED	
					NO.	%	NO.	%	NO.	%	NO.	%
Applicator	724	0	1	0	1	0.14	556	76.8	17	2.4	6	0.83
Tampon	724	2	2	0	4	0.55	502	69.3	10	1.4	3	0.41
Physician	724	4	2	2	8	1.1	310	42.8	5	0.7	1	0.14

Conclusion

It seems that the following conclusions can be drawn from our study of screening of patients in a low socioeconomic group by cervical cytological methods:

1. Almost complete compliance can be obtained by screening by whatever method, applicator, tampon, or direct cervical smear, if applied to the patient immediately as she presents herself.

2. Delayed or appointment screening in these patients, except those who are pregnant attending a prenatal clinic, will give a poor yield, approximately one out of 3 complying.

3. Pregnant patients comply twice as frequently on the same basis.

4. Better results in delayed or appointment screening in nonpregnant patients are obtained in the older age groups.

5. If facilities are limited, screening programs of the delayed or appointment type should be applied to older age groups, in other than pregnant women. Pregnant women should be screened in the prenatal clinic.

6. If the positive smears and the possibly positive smears are considered together, the physician smear is superior.

7. If only the positive smears are considered, all three types of smears were equally efficient.

8. No attempt at determining absolute adequacy was made, since there was no follow-up on the patients with negative smears.

9. The physician-obtained smear showed superiority in adequacy in regard to the number of smears with endocervical cells, and the number with insufficient cells for study.

10. No consideration has been given in this report to the subject of unit cost.

We wish to extend our thanks to Mr. Edward Greene of the Bureau of Adult Hygiene of the New York City Department of Health and to Mr. Louis Pincus of the Bureau of Records and Statistics of the New York City Department of Health for their generous help in arranging this study and analyzing the results.

CASE REPORT OF GYNANDROBLASTOMA

JULIAN WALDO ROSS, M.D., MORRIS A. WEINBERGER, M.D., AND LIONEL A. DESBORDES, M.D., WASHINGTON, D. C.

(From the Department of Obstetrics and Gynecology, Freedmen's Hospital, and the Department of Pathology, College of Medicine, Howard University)

THE term "gynandroblastoma" was first used by Meyer,[1] in 1930, in discussion of a series of arrhenoblastomas reported by him, as one of his cases, in part, bore a histological similarity to granulosa-cell tumor and was accompanied by hypertrophy of the uterus. Plate,[2] in 1938, collected 12 cases of ovarian tumors from the literature, which he believed could be designated as arrhenoblastomas and added one of his own. The tumor, in his case, had both granulosa-cell and arrhenoblastomatous elements.

Since the report by Plate, 2 additional cases of gynandroblastoma have appeared in the literature. Melcher and Black[3] reported one case in 1943. Hobbs[4] reported another in 1948. We wish to report another case of gynandroblastoma encountered in our service.

M. G., No. 138,500, a 70-year-old woman, gravida ii, para ii, was admitted to Freedmen's Hospital on Feb. 4, 1956, with the chief complaint, "I started menstruating." Her last normal menstrual period had been about 30 years before, and menses had always been regular prior to the menopause.

About 5 years before admission, she first noticed the growth of a beard and a moustache which required daily shaving. She noticed also a remarkable return of the libido 2 to 3 years prior to admission. Three months before admission, she began to have pain in the lower left quadrant accompanied by the appearance of bright red vaginal bleeding requiring 9 to 10 pads on some days. This bleeding was intermittent and accompanied occasionally by clots. There were no changes in voice or body contour.

Physical examination on admission revealed an elderly Negro woman who appeared much younger than her stated age. There was demonstrable growth of hair about the chin and lip (Fig. 1). The body contour was that of a normal woman. The blood pressure was 140/80, pulse 80, respirations 20, and temperature 98.6° F.

Pelvic examination disclosed a markedly hypertrophied clitoris measuring 3.5 cm. in length and 1.25 cm. in diameter. There was a left Bartholin cyst about 3 cm. in diameter. The mucosa of the vagina appeared normal and active. Palpation showed the vaginal canal to be constricted by a fibrotic ring distal to the cervix. The cervix was small, clean, slightly softened, normal in color, and practically flush with the vaginal vault. The uterus was slightly enlarged and firm. A huge cystic mass was palpated in the right adnexal region extending about 4 cm. above the umbilicus. A smaller noncystic mass was palpated in the left adnexal region.

Laboratory data showed: hemoglobin, 8.64 Gm. per 100 c.c.; hematocrit, 32; erythrocyte sedimentation rate (Weintraub), 37; 17-ketosteroids, 6.18 mg. per 24 hours.

An endometrial curettage was done on Feb. 10, 1956. The pathologic report was "cystic endometrial hyperplasia." This could account for the arrythmic uterine bleeding

starting 3 months prior to admission. From the history of a beard, moustache, and hypertrophy of the clitoris, the possible presence of a masculinizing tumor of the ovary, or tumor (benign) or hyperplasia of the adrenal cortex had to be considered. Return of the libido together with the development of hyperplasia of the endometrium made the presence of a feminizing tumor of the ovary very likely. These phenomena represented a most unusual bisexual symptomatology.

Laparotomy was performed on Feb. 13, 1956, at which time a uterus with fibroids, both Fallopian tubes, a large cystic structure from the right adnexa, and the left ovary were removed. Appendectomy was also performed. The patient's postoperative course was associated with intractable singultus which was subsequently controlled, and "hot flushes." She was discharged in good condition 3 weeks after the operation.

Pathological Report.—Microscopic examination of the curettings showed endometrial glands irregular in shape and cystically dilated. One large gland contained papillary infoldings. In addition to the cystic glands many smaller irregular glands were present. The epithelial lining of the glands was predominantly pseudostratified and mitotic cells were infrequent. The endometrial stroma varied from compact to moderately loose; its cells were oval or spindle in shape, and it was infiltrated with a moderate number of round cells (Fig. 2).

The uterus measured 8.0 by 7.0 by 5.0 cm. The endometrium was thin and hemorrhagic from recent curettage. On the posterior wall projecting into the lumen was a nonhemorrhagic submucous myoma measuring 1.5 cm. in diameter, and the myometrium contained a few small intramural myomas. The cervix was not remarkable.

Fig. 1.—Photograph of patient's face, showing marked hirsutism, especially of the upper lip and chin.

The left tube was markedly dilated. It measured 13 cm. in length and varied in diameter from 0.6 cm. to 3 cm. at the fimbriated end. There was green purulent material within the distal lumen. The miscroscopic picture was that of chronic suppurative salpingitis. The left ovary was not remarkable.

The right ovary was markedly enlarged, partially cystic, and measured 15 by 9 by 7 cm. The cyst occupied approximately one half the volume of the ovary, measured 10 by 7 by 8 cm., and contained a mucinous fluid. The lining of the cyst was smooth and nonloculated. The noncystic portion of the ovary consisted of a yellow-tan, nodular, and firm tumor mass, 8 by 4 by 5 cm., which was enveloped by a pearly-gray, shaggy connective tissue.

The cystic cavity of the right ovary was lined with tall columnar epithelium with basally placed nuclei and abundant clear cytoplasm rich in mucin. The solid portion of the ovary consisted of neoplastic cells, the majority of which had spindle, oval, angular, or

Fig.. 2.—Low-power photomicrograph of endometrial tissue, showing an increased number of enlarged cystic glands (cystic endometrial hyperplasia). (×35.)

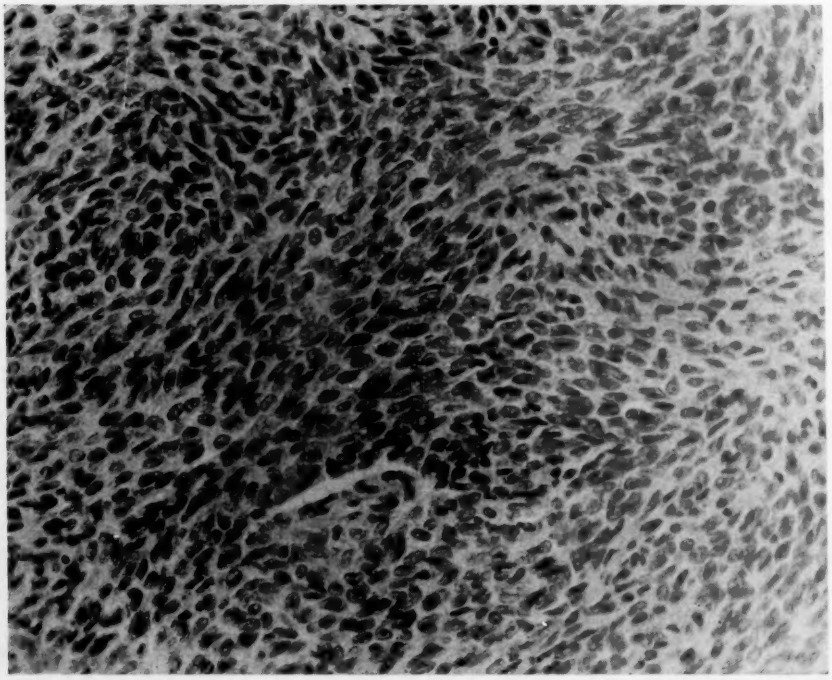

Fig. 3.—Medium-power photomicrograph of tumor, showing predominant granulosa- and theca-cell pattern. (×150; reduced ¼.)

Fig. 4.—Low-power photomicrograph of tumor, showing trabecular pattern at top of photo and granulosa-theca cells at bottom. (×75.)

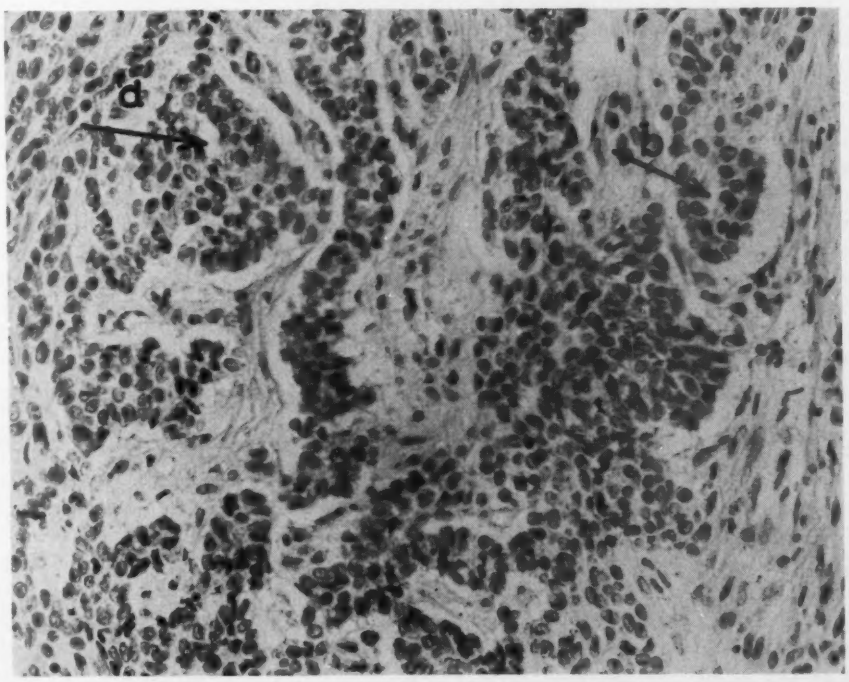

Fig. 4.—Low-power photomicrograph of tumor, showing trabecular pattern at top of photo of arrhenoblastoma. Arrows at *a* and *b* indicate small central lumina in 2 groups of neoplastic cells. (×150.)

irregularly shaped hyperchromatic and clumped nuclei. Pleomorphism and mitotic activity were slight, and the cytoplasm was sparse and eosinophilic. In many areas the cells resembled stromal cells of the ovary, while in other areas they resembled granulosa and theca cells (Fig. 3). The cells tended to be grouped into round or oval nodules, at the periphery of which there was a condensed collagenous connective tissue.

Scattered throughout the tumor were a moderate number of thin-walled vascular channels. Several foci of well-defined, anastomosing and solid epithelial cords with a trabecular pattern were seen (Fig. 4). Several of these cords surrounded tiny cystic spaces suggesting tubule formation (Fig. 5). The pathologic diagnoses were gynandroblastoma and pseudomucinous cystadenoma.

Fig. 6.—Follow-up photograph of patient's face, 16 months post operation, showing marked reduction in hirsutism.

The patient was seen 16 months after operation and there was a striking diminution in hirsutism (Fig. 6). She then shaved once a week, whereas prior to operation she shaved daily. The clitoris appeared to be reduced to approximately one half its preoperative size. The patient reported noticeable regression of the libido.

Summary

A brief historical review of the few reported cases of gynandroblastoma has been cited.

A case has been reported which satisfies the criteria, clinically, endocrinologically, and morphologically for the diagnosis of gynandroblastoma.

References

1. Meyer, Robert: Beitr. path. Anat. 84: 485, 1930.
2. Plate, W. P.: J. Obst. & Gynaec. Brit. Emp. 45: 254, 1938.
3. Melcher, E. A., and Black, W. C.: Am. J. Path. 19: 633, 1943.
4. Hobbs, J. E.: Tr. Am. Gynec. Soc. 71: 57, 1948.

BENIGN CYSTIC TERATOMA OF THE OVARY WITH EXTRACYSTIC SEGMENT OF COLON, AN UNUSUAL CASE*

J. Bernard Bernstine, M.D., and Paul Jernstrom, M.D.,
Philadelphia, Pa.

(From the Departments of Obstetrics and Gynecology, Pathology, and the Clinical Laboratories, Jefferson Medical College Hospital)

BENIGN cystic teratoma of the ovary is the accurate designation for the common neoplasm erroneously termed "dermoid cyst" since these tumors possess tridermal characteristics. We must be resigned to the continued use of the misnomer, dermoid cyst, however, for, as Nicholson[6] stated, "The death of a dogma takes geological time." Willis[13] contended that highly organized structures are sometimes associated with benign cystic teratomas. In addition to digits, phalanges, metacarpals, and neural elements, intestine, possessing all coats as free coils, is encountered. Novak[7] also mentioned that intestinal loops are found in these tumors. A survey of the literature to November, 1957, however, discloses only five references to the occurrence of portions of adult type bowel forming an integral part of benign ovarian cystic teratomas, but all were apparently intracystic in location. [5, 8-11] The following case then, is a unique one of a benign cystic teratoma of the ovary with an extracapsular loop of mature colon.

Clinical Data.—For 3 weeks this 51-year-old, well-developed and nourished white woman complained of intermittent pain in the right flank which radiated posteriorly. It was accentuated when she assumed a reclining posture. The menarche was at the age of 15 years and menstruation was normal thereafter. She was gravida and para iv and had an unremarkable menopause at the age of 48 years. Physical examination disclosed the presence of a large mass in the lower right side of the abdomen. It extended from the level of the umbilicus down into the pelvis, felt cystic and movable. Pelvic examination confirmed the location of the cystic mass which nudged the uterus forward and pulled the cervix up behind the symphysis pubis. Results of laboratory tests were within normal limits. Roentgenographic examinations included an intravenous pyelogram and a barium enema study. A large pelvic soft-tissue mass was seen which reached the level of the fourth lumbar vertebra and contained calcifications suggestive of the presence of bone and/or teeth. The pyelogram showed the right ureter to be definitely displaced laterally around and apparently adherent to the cystic mass. This ureter was dilated from the level of the fourth lumbar vertebra to the brim of the pelvis and was not visualized well beyond this landmark. No intrinsic abnormality of the large bowel was noted in the barium contrast, but there was evidence of external pressure upon the distal sigmoid colon by the pelvic mass with displacement of the cecum up and out of the pelvis. The calcifications within the mass were cited again and the impression was that there was an ovarian tumor, probably a teratoma, in the pelvic cavity on the right side.

*Presented at a meeting of the Obstetrical Society of Philadelphia, Dec. 5, 1957.

Subsequently, a right salpingo-oophorectomy was performed following uterine dilatation and curettage. When the abdomen was opened a large bluish cyst which was within the right broad ligament was encountered; it completely filled the pelvis. The right broad ligament was divided in its upper part and the cyst mobilized and removed. The patient tolerated the procedures well and her postoperative course was uneventful.

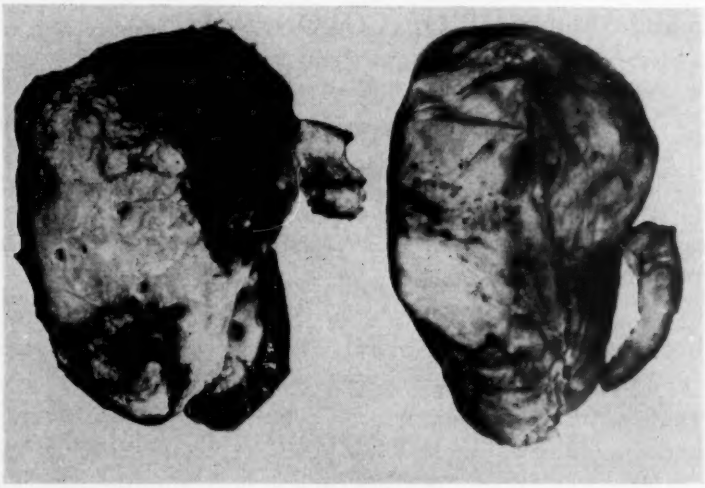

Fig. 1.—Hemisectioned benign cystic teratoma of the ovary with the matted hair on top, the bulk of the contents being pultaceous, sebaceous material. The attached loop of extracapsular bowel is noted on the right.

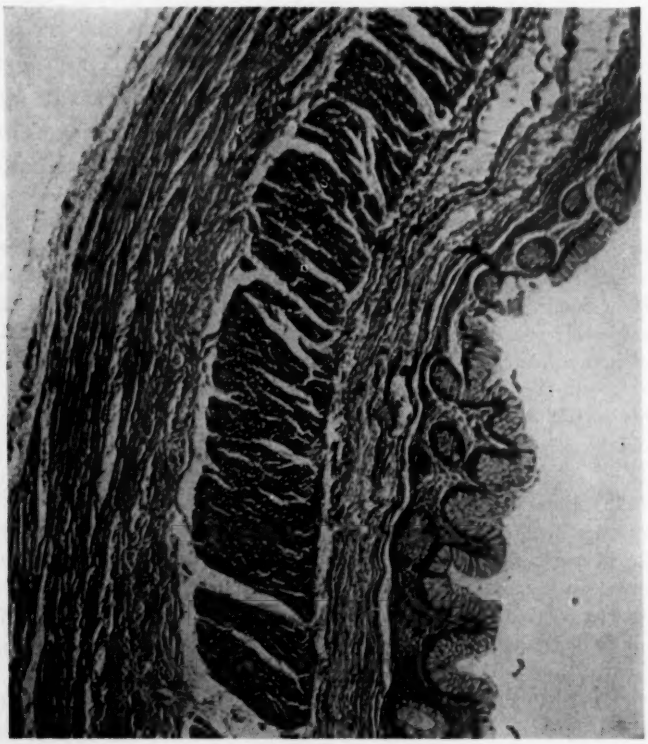

Fig. 2.—The entire thickness of the extracystic segment of mature colon, demonstrating all layers or coats. (×50.)

Gross Pathological Examination.—The specimen consisted of a fresh, large, cystic right ovary which measured 17 by 12.5 cm. and the adherent Fallopian tube. A striking feature of the otherwise gray-pink, smooth, and glistening external surface of the cystic mass was the handlelike attachment of a tubular structure which measured 8 by 1.5 cm. It was fixed to the capsule of the tumor by fibroadipose tissue so that this part of the specimen mimicked a segment of intestine with its mesentery (Fig. 1).

A copious amount of yellow-green, greasy, lardaceous material comingled with abundant dark-brown, coarse hair exuded when the mass was incised. The evacuated cyst had a finely granular, pale pink to yellow-gray internal surface which, in the thicker portions, resembled the skin of the scalp. The wall measured from 0.2 cm., to the part comprising the mammilla or nipple, which was 2.0 cm. thick. The latter area contained a bone-hard core and was surrounded by pink-gray, variegated, firm tissue. Viscid black meconium-like material escaped from the double-blind loop of attached bowel when it was opened. Its mucosa was stained green black and the wall was thin. This feature of the extracapsular loop of bowel is fascinating and lends itself to speculation since there was no biliary structure connected in any way with the specimen to account for the apparently bile-stained meconium-like contents.

Microscopic Examination.—Study of the histologic sections from the mammillary portion of the ovarian cyst disclosed the presence of predominantly cutaneous tissue replete with appendages. Another ectodermal derivative encountered, in addition to the skin, hair, and sebaceous material present, was some retinal tissue of the eye. Mesoderm was represented by foci of cartilage and bone and the entoderm by respiratory epithelium and the colonic mucosa of the extracystic coil of intestine (Fig. 2). Thus, the clinical and gross pathological diagnosis of a benign cystic teratoma of the ovary with an extracapsular segment of mature colon was verified histologically.

Comment

It is significant that authorities like Novak[7] and Willis[13, 14] mentioned that highly organized structures such as free loops of intestine and attached mesentery are sometimes found associated with benign cystic teratomas of the ovary. Perusal of the medical literature, however, discloses only 5 instances in which coils of adult intestine were found, and in each case the bowel originated within the cyst. Pommer,[9] in 1890, described tissue resembling cecum and appendix within a cystic ovarian tumor. Shattock,[12] in 1904, reported finding, in addition to poorly developed lower limbs and a vulva with pubic hair, coils of intestine in a celomic cavity. Andrews,[1] in 1912, mentioned the presence of a tubular structure attached to a mesentery projecting from the inner lining of an ovarian cystic tumor. It was gut and even contained nerve ganglia in its coats. Schoenholz,[10] in 1923, discovered a double-blind loop of large intestine, one end of which was attached to the dermoid plug and the other to the cyst wall. The gut hung outward into the carrier's abdomen through a cleft in the cyst, apparently a defect in its wall. Schottenfeld and Littauer,[11] in 1938, also reported a cyst of the ovary containing an appendix and portion of ileum attached to the inner surface. Willis[13] cited several cases wherein segments of intestine were found associated with benign cystic teratomas involving tissues and organs of the body other than the ovary, such as the sacrococcyx. The case herein presented, then, is, to the best of our knowledge, the first describing the presence of a segment of mature intestine attached to the external surface (extracystic) of a benign cystic teratoma of the ovary.

Summary

A tumor is described that is believed to be the first example of a benign cystic teratoma of the ovary with an extracystic segment of mature colon. The clinical, roentgenographic, and gross and microscopic pathologic aspects of benign cystic teratomas of the ovary are reviewed.

We wish to thank Margaret Endel for the illustrations and Regina Nekludov for the histologic preparations.

References

1. Andrews, H. R.: Proc. Roy. Soc. Med. **62**: 54, 1912.
2. Blackwell, W. J., Dockerty, M. B., Masson, J. C., and Mussey, R. D.: Am. J. Obst. & Gynec. **51**: 151, 1946.
3. Colcock, B. P., Sass, R. E., and Standinger, L.: New England J. Med. **252**: 373, 1955.
4. Frank, R. T.: Gynecological and Obstetrical Pathology, ed. 2, New York, 1931, D. Appleton and Company, p. 361.
5. Herbut, P. A.: Gynecological and Obstetrical Pathology, Philadelphia, 1953, Lea & Febiger, p. 389.
6. Nicholson, G. W.: Studies on Tumor Formation, St. Louis, 1950, The C. V. Mosby Company.
7. Novak, E.: Gynecologic and Obstetric Pathology, ed. 3, Philadelphia, 1952, W. B. Saunders Company, p. 442.
8. Peterson, W. F., Prevost, E. C., Edmunds, F. T., Hundley, J. M., Jr., and Morris, F. K.: Am. J. Obst. & Gynec. **70**: 368, 1955.
9. Pommer, C. P.: Quoted by Ewing, James: Neoplastic Diseases; A Treatise on Tumors, Philadelphia, 1940, W. B. Saunders Company, p. 676.
10. Schoenholz, L.: Zentralbl. Gynäk. **43**: 1363, 1923.
11. Schottenfeld, L. E., and Littauer, E. V.: Am. J. Obst. & Gynec. **35**: 889, 1938.
12. Shattock, P. E.: Lancet **2**: 1284, 1904.
13. Willis, R. A.: Pathology of Tumours, London, 1948, Butterworth & Co., Ltd.
14. Willis, R. A.: Teratomas in Armed Forces Institute of Pathology, Atlas of Tumor Pathology, Section III, Fascicle 9, Washington, D. C., 1951, pp. 9-37.

MESOTHELIOMA OF THE PELVIC PERITONEUM RESEMBLING PAPILLARY CYSTADENOCARCINOMA OF THE OVARY

Case Report

MARTIN SWERDLOW, M.D., CHICAGO, ILL.

THIS case presents highly suggestive evidence for the primary origin of a tumor from the pelvic peritoneum.

The patient was a 27-year-old white woman whose complaints were pelvic pain, frequency and urgency of urination, and a feeling of heaviness in the lower abdomen of 8 years' duration. These symptoms had increased in severity during the past 2 years.

Examination revealed a firm, tender, but freely movable mass in the left adnexal region of the abdomen. X-ray examination of the abdomen disclosed a calcific mass in the pelvis; a retrograde pyelogram demonstrated a distortion of the urinary bladder. The laboratory findings were noncontributory.

Exploratory laparotomy was performed and a friable, oily, and granular tumor was found which compressed the urinary bladder, but was attached to it only by loose filmy adhesions. Similar adhesions bound the tumor to the fundus of the uterus. By contrast the tumor was densely adherent to the mesentery of the transverse colon and urachal region and almost completely surrounded the peritoneal surface of the left uterine tube. The right tube was not involved and was grossly free of changes *as were both ovaries.* The tumor was removed as completely as possible and careful examination showed no other tumor masses in the abdominal cavity or in any of the viscera within it.

Pathological Description.—Grossly the tumor was very friable, granular, irregular, yellowish tan, and measured 8.5 by 7.0 by 5.0 cm. Attached to one portion of the mass was a distended tubular structure which, opened, revealed no gross changes although the tumor mass in places completely surrounded this uterine tube. The cut surface of the tumor mass was finely and uniformly granular, soft, and focally hemorrhagic (Fig. 1).

Microscopically, under the lowest power, the tumor superficially, but in striking fashion, resembled placental tissue (Fig. 2). The tumor for the most part consisted of variable-sized papillae cut in cross section, and in an occasional field cut longitudinally. These papillae were vaguely divided into lobules by elongated strands of vascularized fibrous connective tissue. The roughly oval and circular papillae generally appeared to be lying free in space.

The papillae were surrounded by a single layer of columnar to cuboidal cells with fairly distinct cell borders. In places these cells were closely packed, piled up, and appeared pseudostratified, and in some fields they were ciliated. Cells in mitosis were only rarely seen. The stroma of the papillae varied from loose and edematous, infiltrated with lymphocytes, plasma cells, and occasional granulocytes, to a denser stroma with prominent stellate fibroblasts. There were all variations in between. Most striking were the concentric small and larger depositions of calcified psammoma-like bodies which occupied the most central portion of almost every papillary structure. In places these calcified bodies were but droplets and in other places they formed amorphous flowing masses which ulcerated the epithelial covering of the papillae (Fig. 3). In general, they formed circular bodies lying in the center of the papilla. The centers of occasional papillae contained cysts filled with

eosinophilic edemalike fluid and were lined by cuboidal to flat cells. In some fields the calcified bodies were lying free, obviously extruded from ruptured papillae. Some sections revealed papillae and free-lying calcific bodies in the peritubal connective tissue. The uterine tube itself showed no other pathologic changes. One section revealed a multiloculated cystic structure lying adjacent to the uterine tube and surrounded by tumor. The cyst was lined by typical endometrial epithelium which covered typical endometrial stroma, embedded in which were typical endometrial glands. The cystic space was filled with blood and its epithelial lining in an occasional field very closely resembled the epithelial covering of the papillae.

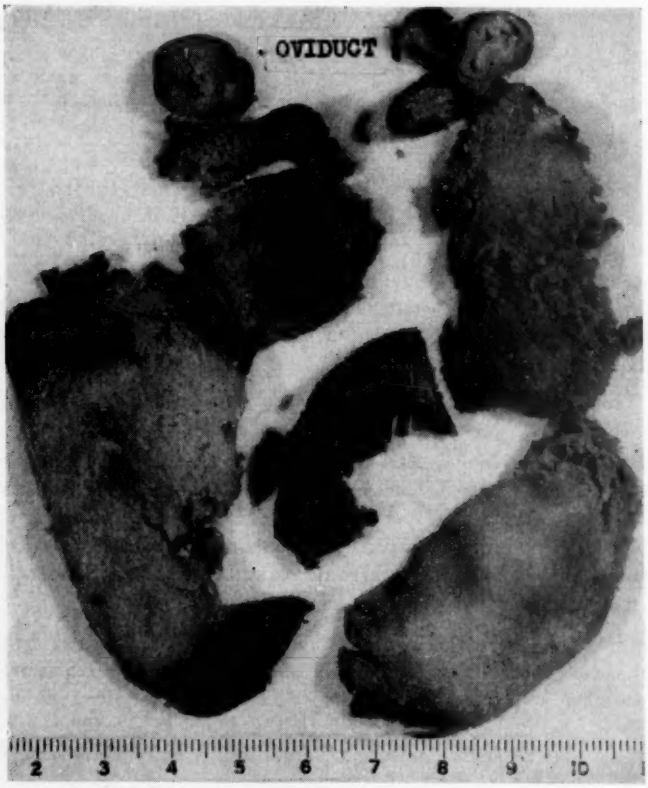

Fig. 1.—Cut surface of gross tumor previously fixed. Note finely granular "sandy" appearance.

Comment

The tumor histologically resembled a papillary cystadenocarcinoma of the ovary. The ovaries, however, were found to be free of changes at the time of the exploratory laparatomy. It must be admitted that underlying this entire discussion is the outside possibility of a yet undisclosed small primary tumor within one of the ovaries or even a more distant primary tumor, the attending surgeon's statements to the contrary.

The possible organs and tissues of origin, excluding the ovaries, capable of giving rise to such a tumor are those whose embryological development is similar to that of the ovary—the uterine tubes, uterus, and the pelvic peritoneum.

The uterine tubes seemed an unlikely possibility because the right was entirely uninvolved and the left although embedded in places in tumor showed no involvement of the mucosa by tumor. There was no direct connection of the uterus to the tumor and at the time of operation the uterus was small,

firm, and grossly free of changes. Biopsy of the cervix some months before showed a chronic cervicitis. To our mind, this left but one other local possibility, viz., the pelvic peritoneum.

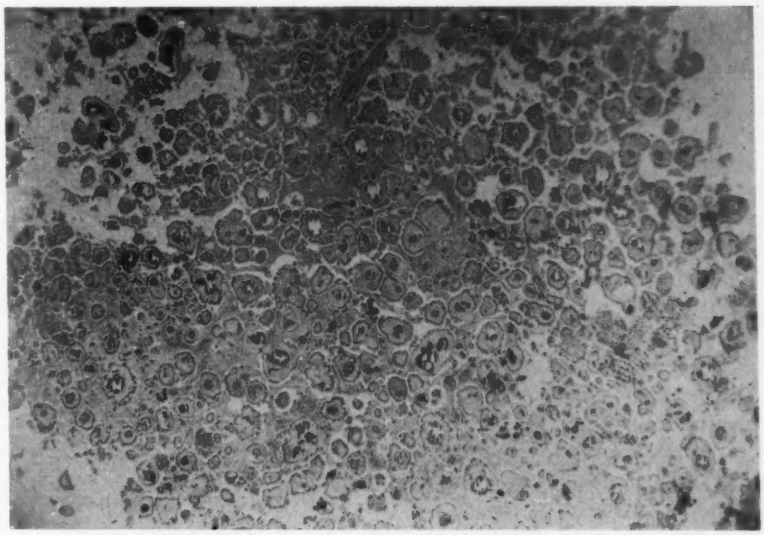

Fig. 2.—Low-power view of tumor. Note innumerable papillae and superficial resemblance to placental tissue. (×35.)

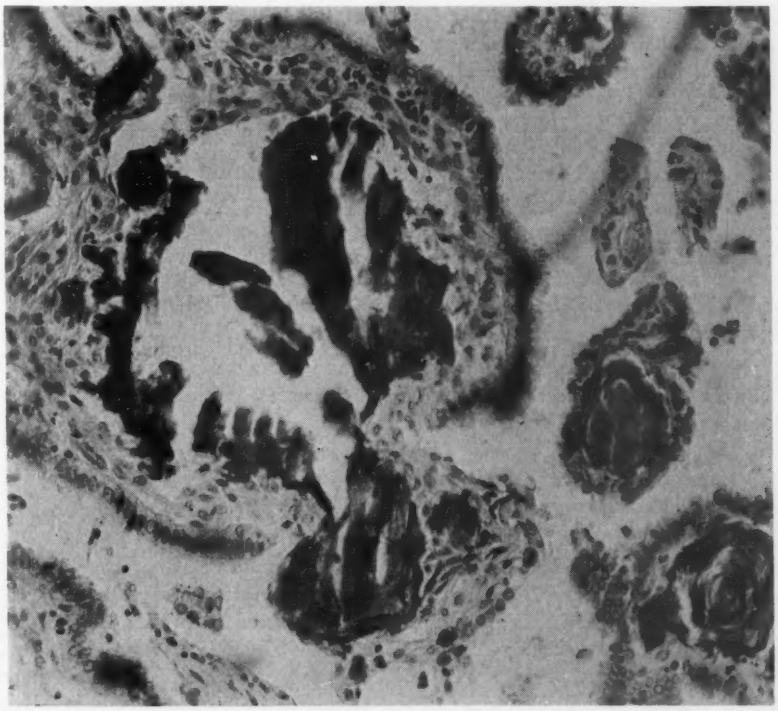

Fig. 3.—Papillary structures of varying size with central "psammoma" bodies. (×450.) (No. 53S 3109. U. S. Army—Central Photography Laboratory, Presidio of San Francisco, California.)

It has been pointed out by many people that the germinal epithelium of the ovary represents the original celomic epithelium with most of its differentiating

potency unused and stored.[3] Embryologically there also appears to be no essential difference between the germinal epithelium of the ovary and the pelvic peritoneum.[1] It is felt that this potential for differentiation or totipotentiality in postnatal and adult life can, through metaplasia, recapitulate and develop all of the epithelial components of the Müllerian system, namely, tubal epithelium, endometrium (celomic metaplasia theory of endometriosis), and endocervical epithelium.

In this case it is our feeling that some influence, perhaps inflammatory, perhaps hormonal, caused the "genitally ripe" pelvic peritoneum with its stored "embryonic" potential to differentiate or resume its embryonic role and in one instance to produce the endometrial cyst observed and in another instance to dedifferentiate and produce the papillary tumor. There is also the possibility that this papillary tumor was preceded by the formation from the pelvic peritoneum of some other type of "ovarian" cyst such as a serous papillary or nonpapillary cystoma or pseudomucinous cystoma, papillary or nonpapillary.

Our feelings are based on this inherent potentiality of the celomic mesothelium to differentiate into the tissues to which it was embryologically capable of giving rise; and as an extension of this potential, under certain not well-understood circumstances to give rise to the same benign and malignant tumors to which the adult derivatives, ovaries, tubes, and uterus, are subject.

Hertig[2] has presented a case almost identical to this one, in a 27-year-old woman, and called it "papillary carcinoma" of the pelvic peritoneum (papillary mesothelioma). In commenting on this case he remarked that he took a very dim view and trusted very little what the pelvic peritoneum did when it started to grow in tumor formation, that this particular tumor was no worse in appearance than some papillary cystomas of the ovary which ultimately grow more malignant and cause the death of the patient.

Summary

A case is presented in which a papillary tumor with psammoma bodies resembling ovarian carcinoma is felt to have arisen from the pelvic peritoneum.

References

1. Arey, L. B.: Developmental Anatomy: A Textbook and Laboratory Manual of Embryology, ed. 4, Philadelphia, 1942, W. B. Saunders Company.
2. Hertig, A. T.: Proc. 18th Seminar, American Society of Clinical Pathologists, Chicago, Oct. 17, 1952, pp. 49-53.
3. Novak, E.: J. Mount Sinai Hosp. 14: 529, 1947-1948.

AN UNUSUAL ADENOCARCINOMA OF THE OVARY*

A Case Simulating Schiller's "Mesonephroma"

J. T. DUHIG, M.D., BOSTON, MASS.

(From the Laboratory of Pathology, Harvard Cancer Commission and the Cancer Research Institute, New England Deaconess Hospital)

IN 1939 Schiller[7] described a group of ovarian tumors whose histology was characterized by the appearance of glomerulus-like formations and structures resembling abortive renal tubules. The epithelium of these glomeruli and tubules was said to be of characteristic "hobnail" appearance. To such tumors, he assigned the name mesonephroma ovarii in the belief that they arose from mesonephric remnants in the ovary. Subsequently several papers appeared in which similar groups of tumors were described[3, 4] but in all of which the authors considered Schiller's suggested mesonephric origin of the growths to be either doubtful or unproved.

The present report is that of a tumor containing areas indistinguishable from those seen in the so-called mesonephroma ovarii but in which areas of quite definite adenocarcinoma could be identified, together with structures resembling the "embryoid" bodies seen in many testicular tumors of teratomatous or embryonal carcinomatous type.[2]

Case Report

Clinical History.—The patient was a married woman aged 44 years. She had one child aged 7 years, and a clear obstetric history. On her admission to the hospital, she complained of irregular vaginal bleeding for some years which had become worse during the previous 2. Her menses were usually regular, covering 7 to 10 days of a 28 day cycle and they were frequently accompanied by dysmenorrhea. Five days prior to admission a dull aching pain had commenced in the left upper quadrant of the abdomen and this had gradually increased in severity. She had also noted a gradual increase in the size of the abdomen over the preceding 2 days. Examination disclosed a large tumor almost filling the abdomen. A diagnostic x-ray of the region showed a large soft-tissue mass displacing bowel, the appearance suggesting a cyst arising from the lower abdomen. The diagnosis was uncertain but cysts of pancreatic, mesenteric, or ovarian origin were considered.

At laparotomy, a large intraperitoneal tumor was displayed which had a pedicle attaching it to the right broad ligament and which appeared to have replaced the right ovary. The tumor was removed together with the right Fallopian tube. The patient made an uneventful recovery. When it was learned that the tumor was a malignant one, hysterectomy, left salpingectomy, and left oophorectomy were performed. At this operation, one month following the laparotomy, several groups of large, hard para-aortic glands were felt, which had the appearance of secondary deposits. In view of the presence of these abdominal metastases, deep x-ray therapy was instituted. Initially, this was directed at the abdomen

*This work was commenced in the Pathology Department, General Hospital, Brisbane, Australia.

but 3 months later when secondary masses began to appear in the supraclavicular region, a course of radiation was aimed at eliminating these. This therapy appeared to have little effect on the secondary tumors and a large abdominal mass soon appeared. The patient now began to suffer some respiratory distress and secondary mediastinal deposits appeared. It was from these that she finally died, 9 months after the removal of the primary tumor. No autopsy was permitted.

Gross Pathology.—As no autopsy was allowed, description of the lesions found must necessarily be confined to those removed at operation. The ovarian tumor was a large encapsulated growth measuring 18 by 17 by 11 cm. in its largest diameters and weighing 1,616 grams. It was covered by a smooth, glistening, grayish-colored capsule which appeared to be almost complete; at one pole of the tumor an area of more exuberant growth was noted which had produced marked thinning of the capsular tissue and multiple small nodules of tumor tissue could be seen just beneath this surface. Many large, dilated blood vessels coursed over the external surface of the tumor and some thick fibrous strands which had formed adhesions between the growth and the surrounding tissues were present. No definite evidence of the right ovary could be demonstrated but the attached Fallopian tube was seen stretched across the outer aspect of the tumor capsule. The remaining pelvic organs showed no macroscopic evidence of pathologic change.

Cross section of the tumor showed its greater part to be composed of a solid reddish-brown material not unlike fixed liver tissue. One portion of the tumor consisted of a large degenerate mass of white, almost caseous material which showed some old and recent hemorrhages and the dark solid portion of the tumor also appeared to contain much hemorrhagic tissue. Toward the periphery of the growth, tumor tissue appeared better preserved and there were seen islands and tongues of pale yellow tissue extending into the darker hemorrhagic mass. At one pole, there was a small projecting nodule which appeared to represent the remaining ovarian tissue. There were a few foci of cyst formation, some obviously having been formed as a result of necrosis and liquefaction of tumor tissue, but others seemed to be related to the neoplastic process. These cystic foci did not form a feature of the tumor which was mainly of the solid type. In places, the tumor was transected by fibrous septa, which in most cases appeared to carry a vascular bundle. No papillary formations were noted and there was no pseudomucinous secretion.

Microscopic Findings.—The histologic appearance of the tumor was quite striking and a number of stains were used in its study. These included the periodic acid-Schiff technique, Mallory's phosphotungstic acid-hematoxylin, Masson's trichrome stain, and hematoxylin and eosin. The neoplastic structures appeared to have become grouped into units within the growth, each unit being supported and surrounded by a connective tissue stroma and separated one from the other by much hemorrhagic necrotic material. Each of these neoplastic units was made up of one or more of three commonly found components. These were defined as follows: (1) moderately well-differentiated carcinomatous glands, (2) structures resembling fetal glomeruli with associated tubular channels, and (3) small discrete cystic formations resembling mammalian embryos.

Collections of frankly carcinomatous glands were scattered through the tumor (Fig. 1) and often they were the only structures seen in the small neoplastic units. The tall columnar carcinoma cells composing these structures were seen to be reduplicated in the glomeruloid and embryoid lesions and, in the great majority of cases, the latter two seemed to have developed from the carcinomatous structures. The glomeruloid lesions appeared to have been derived through a definite succession of stages which could be followed in

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Fig. 1.—Focus of adenocarcinoma in edematous, hemorrhagic stroma. (Hematoxylin and eosin. ×150; reduced ⅓.)

Fig. 2.—Top, center, and right, structures resembling fetal glomeruli. Note epithelium bulging into capsular space. The tuft on the right has been cut transversely. Top left, early and, bottom left, intermediate stages in the formation of these glomeruloid structures. (Hematoxylin and eosin. ×150; reduced ⅓.)

Fig. 3.—Pseudotubule lined by bulging "hobnail" epithelium. (Periodic acid-Schiff-hematoxylin. ×1,000; reduced ⅓.)

Fig. 4.—Formation resembling early mammalian embryo. (Hematoxylin and eosin. ×400; reduced ⅓.)

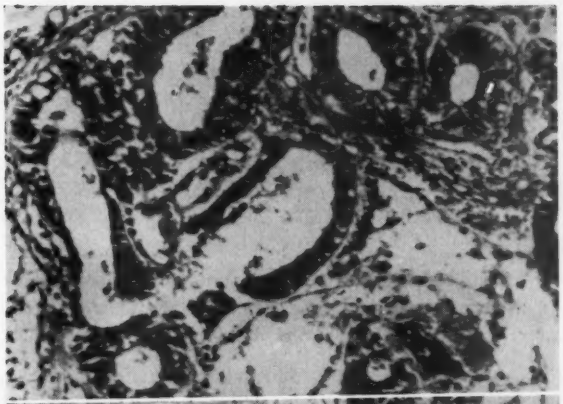

Fig. 1.

Fig. 2.

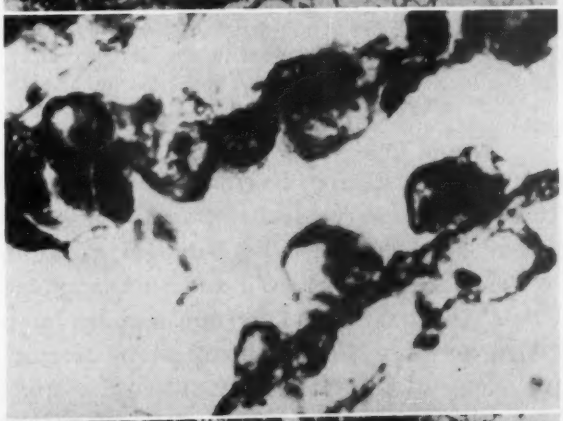

Fig. 3.

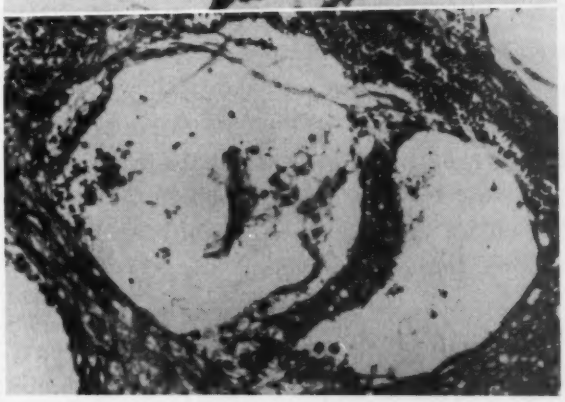

Fig. 4.

Figs. 1-4.—*For legends see opposite page.*

different portions of the tumor. Two fully formed glomeruloid lesions with intermediate stages in their formation are illustrated in Fig. 2. The process of formation of these structures appeared to consist of invagination of a carcinomatous gland space by a knot of vessels derived from the connective-tissue stroma. The cells destined to form the capsule of the glomeruloid structure appeared to undergo a flattening process, while those covering the capillary tuft became heaped up, their nuclei bulging prominently into the capsular space. In places, the cells retained their pseudostratified appearance, in others a single layer of cells was all that covered the vascular core of the tuft. Occasional foci of pseudotubule formation were seen and Fig. 3 shows the bulging "hobnail" nature of the epithelium lining these structures.

The third common component of the tumor units, the embryoid bodies, also appeared to be derived from carcinomatous epithelium although this was frequently not as obvious as the derivation of the glomeruloid lesions. As Fig. 4 shows, the resemblance of these structures to early mammalian embryos is quite marked. The spurious ectodermal plate with its underlying mesoderm and entoderm is quite well defined and the amniotic cavity and yolk sac also appear to be formed as distinctive structures. In most cases the cells forming this ectodermal plate are quite patently those of the carcinomatous elements. Adjacent to these bodies, cells resembling syncytial giant cells were occasionally seen suggesting some type of abortive chorionic development.

A small surviving rim of normal ovarian tissue was seen in portions of the periphery of the growth. Much of the stroma of the tumor was edematous and hemorrhagic and a large part of the tumor, particularly its central portion, had undergone complete necrosis. Occasionally small collections of cysts containing serous fluid were seen. Multiple sections failed to reveal any malignant proliferation of other tissues and there was no development of organs or tissues foreign to the ovary which might have suggested that the tumor was a teratoma. The remaining pelvic viscera showed no evidence of neoplasia and no invasion by metastases from the ovarian tumor. The appearances were those of a primary neoplasm of the ovary and there was no evidence to suggest that the tumor was a secondary deposit.

Comment

The formation of glomerulus-like lesions and abortive tubular structures where the cells covering the glomerular tufts and lining the tubules exhibit a "hobnail" pattern have been described by Schiller[7] as being characteristic of his mesonephroma ovarii. The glomeruloid and tubular structures seen in this case were identical with those described by him and by later authors.[9] There were several objections, however, to the classification of this tumor as a "mesonephroma." First, many of the glomerulus-like units appeared to have been derived directly from carcinomatous glands. Second, the appearance of the embryoid bodies suggested that they were derived from the same source but with some variation in their line of differentiation, i.e., instead of a knot of vessels completely invaginating a carcinomatous gland, they tended to become one large vascular space and assumed the appearance of an embryonic yolk sac. Third, there is uncertainty as to whether Schiller's "mesonephroma" really constitutes an entity and, if it does, many authors[6] doubt its suggested origin from mesonephric tissues.

Study of the structures seen in this tumor suggests that a variety of appearances may be produced by a rapidly growing carcinoma of the ovary and one of these is the appearance of structures closely resembling fetal glomeruli. Willis[10] has noted a similar occurrence in tumors of the breast, thyroid, prostate,

and kidney, while Lehmann and Shallock[5] considered the occurrence of glomerular structures in ovarian tumors to be fortuitous and that the term "mesonephroma" should be used in a descriptive sense only, to characterize tumors of the ovary exhibiting this curious differentiation. Glomeruloid structures and embryoid bodies have been observed in certain cases of embryonal carcinoma of the testis[1, 9] and some teratomas of the testis.[2] As Teilum[8] has pointed out, tumors of the ovary and testis are frequently homologous and the structures seen in the present tumor mimic quite closely those seen in the testicular tumors described by him.

It seems preferable, therefore, to classify a neoplasm of this type as an adenocarcinoma of the ovary of embryonal type and to refrain from the use of the term "mesonephroma" with its connotation of a mesonephric rest origin for tumors exhibiting this unusual form of differentiation, when more conventional tissues of origin for the neoplasm appear more likely. Further, it may be noted that the presence of embryoid bodies showing close resemblance to those described in testicular tumors by other authors,[1, 2, 9] illustrates once again the frequent similarity of certain ovarian and testicular neoplasms. The significance of this in the histogenesis of gonadal cancer awaits elucidation.

Summary

A case of adenocarcinoma of the ovary is presented which showed three forms of differentiation. These are described as (1) adenocarcinomatous elements, (2) glomeruloid structures, and (3) embryoid bodies.

It is postulated that the glomeruloid structures arose from carcinomatous glands in the tumor, rendering a mesonephric concept of their origin unnecessary.

The occurrence of embryoid bodies illustrates the close resemblance of certain primitive ovarian and testicular tumors.

My thanks are due to Dr. A. W. Pound for advice and to Dr. A. D. D. Pye for permission to use hospital records.

References

1. Dixon, F. J., and Moore, R. A.: Cancer 6: 427, 1953.
2. Evans, R. W.: J. Clin. Path. 10: 31, 1957.
3. Jones, H. W., and Jones, G. E. S.: Arch. Path. 33: 18, 1942.
4. Kazancigil, T. R., Laqueur, W., and Ladewig, P.: Am. J. Cancer 40: 199, 1940.
5. Lehmann, W., and Shallock, G.: Arch. Gynäk. 181: 222, 1952.
6. Novak, E.: Gynecologic and Obstetric Pathology, ed. 3, Philadelphia, 1952, W. B. Saunders Company, p. 360.
7. Schiller, W.: Am. J. Cancer 35: 1, 1939.
8. Teilum, G.: Acta path. et microbiol. scandinav. 23: 242, 1946.
9. Teilum, G.: Acta path. et microbiol. scandinav. 27: 249, 1950.
10. Willis, R. A.: Pathology of Tumours, ed. 2, London, 1953, Butterworth & Co., Ltd., p. 507.

A TOTAL CARE PROGRAM FOR ADVANCED PELVIC MALIGNANCY*

ALVIN F. GOLDFARB, M.D., AND MARTIN L. STONE, M.D.,
NEW YORK, N. Y.

(From The Department of Obstetrics and Gynecology, New York Medical College-Metropolitan Medical Center)

TO THE Gynecologic Cancer Service at the New York Medical College, Metropolitan Medical Center, a large number of patients who have had previous specific cancer therapy are referred for so-called terminal care. The presence of this somewhat unique group of patients has stimulated our interest in the problems of advanced pelvic malignancy.

It is clinically apparent that these patients have gross metabolic disturbances even though essential organ systems such as the gastrointestinal tract are not involved. The factors contributing to metabolic disturbances in malignancy have been clearly outlined by Myers[1] and may be summarized as follows: (1) those related to the presence of tumor in certain organ systems; (2) those produced by substances which have been elaborated by tumors; (3) those related to the rapid anabolism and catabolism of tumor tissue; and (4) those related to the treatment of neoplastic disease.

A composite of the metabolic disturbances seen in over 200 patients with advanced pelvic cancer showed that these patients had secondary anemia, hypoproteinemia, reversal of the albumin/globulin ratio, and negative nitrogen balance. In addition there were weight loss, malaise, and cachexia.

Our attempts at improving the over-all condition of these patients led to the development of a total care program and the crystallization of certain concepts of management. This program has been described in detail for over 200 patients in another report.[2] Essentially it involves three phases as shown in Table I.

TABLE I. COMPONENTS OF THE TOTAL CARE PROGRAM

Anti-neoplasm Therapy.—
a. Radiation
b. Surgery
c. Chemotherapy
Supportive Care.—
a. Antibiotics
b. Adequate nutrition
c. Anabolic agents
Psychosocial Care.—
a. Social service
b. Occupational therapy
c. Home care service

*This study was supported in part by the Division of Cancer Research and Control, New York City Department of Health.

At present we will confine our remarks to that portion of our program concerned with supportive care with emphasis on nutritional factors and the use of anabolic agents. When this program was started the only available anabolic agent was testosterone. Kochakian and Murlin[3] in 1934 first reported the nitrogen retention effect in castrated dogs following the injection of an extract of urine from male medical students. Kenyon and associates[4] in 1938 demonstrated this effect in humans. In the 20 years which have elapsed many other authorities have confirmed the anabolic activity of testosterone and its derivatives. These reports, however, also emphasized the problems of salt and water retention and the possibility of masculinization in the female. In 1953 Hershberger and co-workers[5] reported on the anabolic activity of a 19-nor-testosterone derivative that had very little androgenic activity. In 1956, the Geriatric Section of the Gynecology Service at our institution undertook a

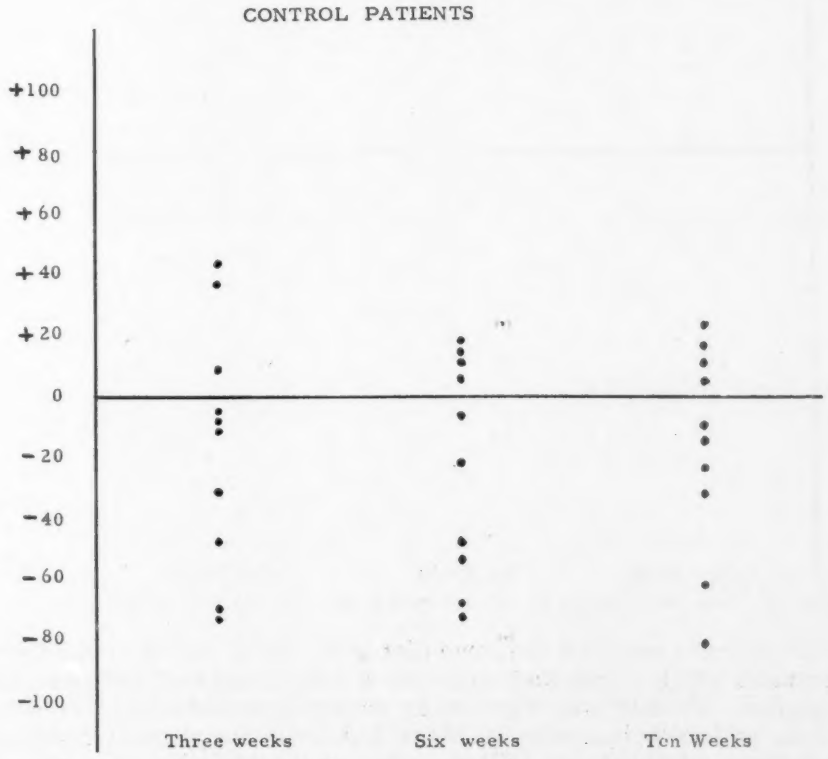

Fig. 14.—Per cent change in urinary nitrogens. Control patients.

detailed evaluation of this newer anabolic agent. The results of this study[6] indicated that this synthetic steroid when used in the geriatric gynecology patient had all the anabolic advantages of the androgens without the side effects of salt and water retention or masculinization. Laboratory studies that were carried out indicated urinary nitrogen retention in all patients. In view of these results, the patients on the Cancer Service were placed on this agent. In order to evaluate its effect more objectively on this group of patients a more detailed laboratory and clinical study was carried out on a small study group.

Material and Methods

The patients being used for this study were selected from the Cancer Service of the Department and had advanced pelvic malignancy as evidenced by recurrences or extension beyond the primary site. The 30 patients in this study were divided into three equal groups for a study period of 10 weeks. One group received no anabolic agent, one group received testosterone, and one group received norethandrolone, a 19-nortestosterone derivative.*

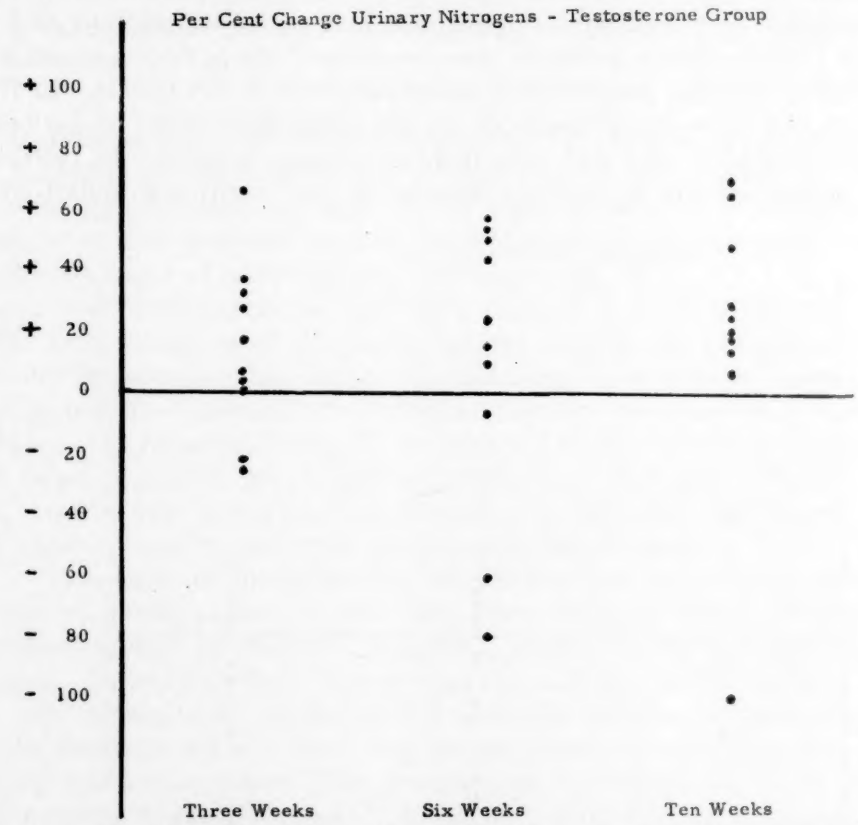

Fig. 1*B*.—Per cent change in urinary nitrogens. Testosterone group.

Diet.—All patients received the same diet in so far as can be controlled on a general hospital ward. This diet calls for a daily intake of between 2,040 and 2,510 calories. Protein was supplied in amounts of 85 to 100 Gm., fat of 100 to 130 Gm., and carbohydrates of 200 to 235 Gm. Supplemental vitamins and minerals were administered in twice the amount of the daily minimal requirements.

Anabolic Agents.—One group received testosterone propionate, 100 mg. daily intramuscularly, for a total weekly dose of 500 mg. The second group of 10 patients received norethandrolone, 25 mg. daily by injection, for a total weekly dose of 125 mg.

Evaluation

The patients were evaluated from both laboratory and clinical standpoints. The following laboratory determinations were performed at the beginning of the study and again at 3, 6, and 10 week intervals during the study period:

*The norethandrolone used in this study was supplied as Nilevar by Dr. J. Wm. Crosson, G. D. Searle and Co., Chicago, Ill.

(1) urinary nitrogen determinations on a 48 hour specimen; (2) urinary creatinine studies on a 48 hour specimen; (3) total serum proteins; (4) electrophoretic patterns; and (5) serum calcium and phosphorus levels.

Clinical evaluation of the patients was based on weight change, response to environment, and changes in narcotic requirements.

Results

1. Nitrogen Balance.—The urinary nitrogen studies revealed no change in nitrogen excretion in the control group (Fig. 1*A*). In the study groups there

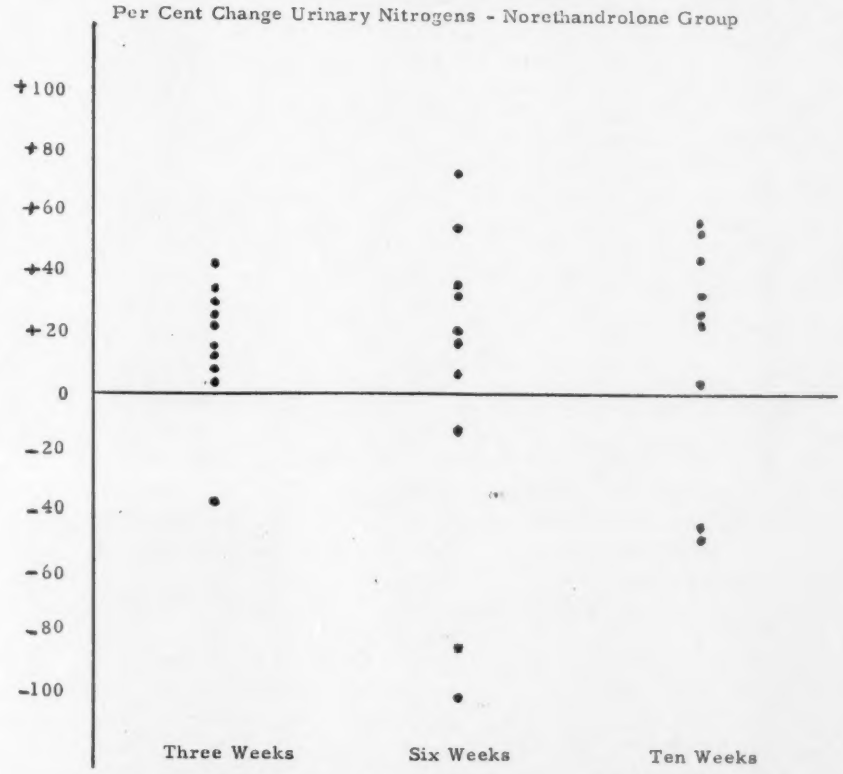

Fig. 1*C*.—Per cent change in urinary nitrogens. Norethandrolone group.

was a marked increase in the amount of nitrogen being retained by the body. This change was shown by both groups (Figs. 1*B* and 1*C*). It is interesting to note that the per cent change in both groups is basically the same. This seems to indicate that both steroids have the same anabolic activity.

2. Creatinine.—The creatinine determinations were performed only to serve as a check on the accuracy of the urinary nitrogen values obtained.

3. Total Proteins.—The change in total proteins while suggestive of an increase was not particularly significant in the study group. There was, however, a definite correction of the reversed albumin/globulin ratio with an increase in the albumin fraction.

4. Electrophoretic Patterns.—Twelve of the 20 patients in the experimental group showed definite evidence of an increase in the albumin fraction in the electrophoretic patterns. At the same time a decrease in the gamma globulin fraction was also demonstrated. Representative changes are demonstrated in Fig. 2.

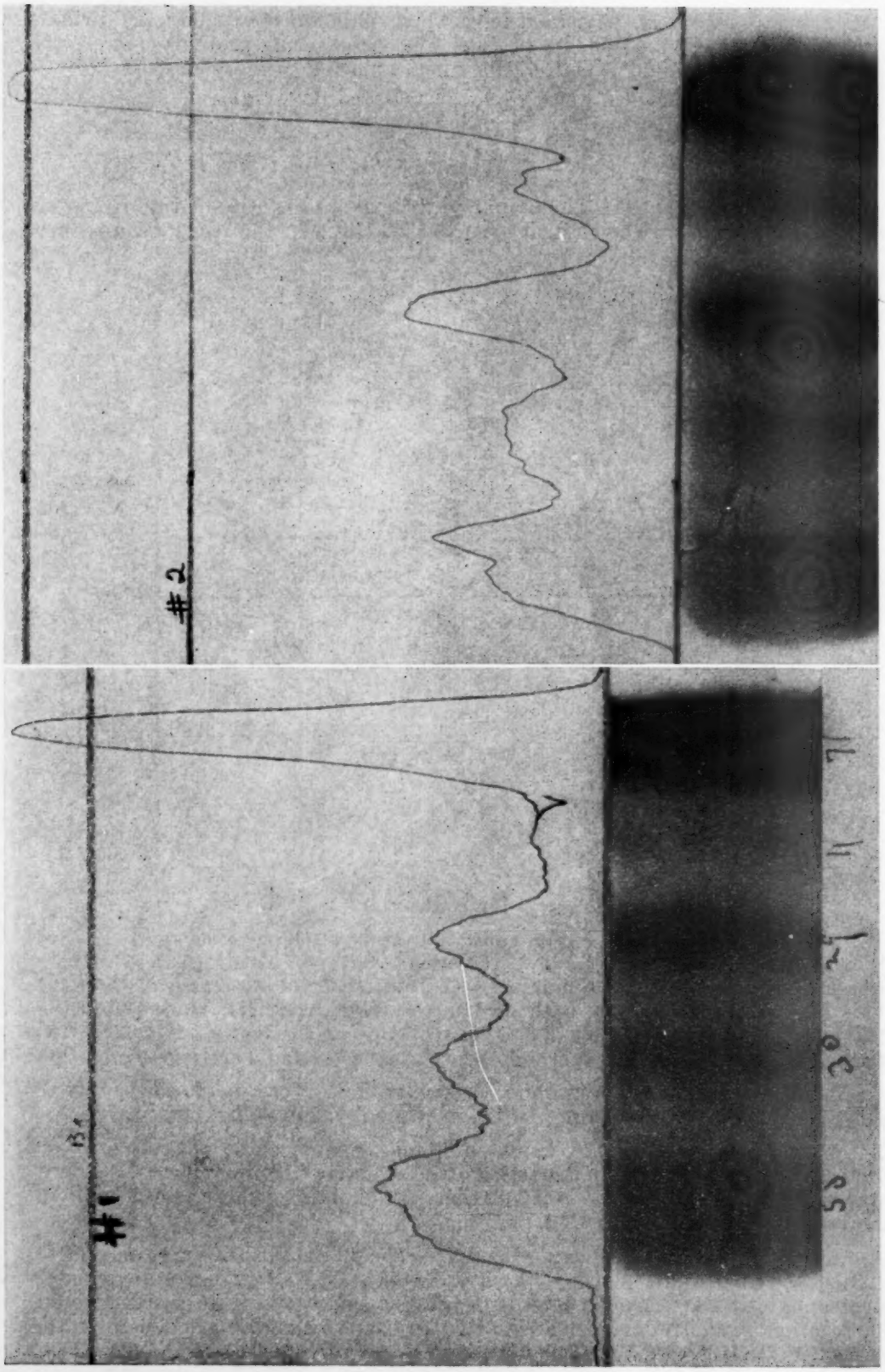

Fig. 2.—Electrophoretic patterns after anabolic therapy showing increase in the albumin fraction.

5. Calcium and Phosphorus.—There were no demonstrable changes in the serum calcium and phosphorus levels.

Table II gives a composite picture of the results following the use of proper nutritional support and anabolic agents.

TABLE II. RESULTS

	PRIOR TO TREATMENT	AFTER TREATMENT
Hemoglobin	8-9.0 Gm.	9-11.5 Gm.
Urinary nitrogen	Negative balance	Positive balance
Total protein	Low	Slightly increased
Gamma globulin	Hypergammaglobulinemia	Normal
A/G ratio	Usually reversed	Normal
Weight		3-5 pound gain

Clinically, 18 of the 20 patients in the study group showed a weight gain of from 3 to 5 lbs. There was a marked increase in appetite and a most favorable response to their surroundings. They were more cheerful and undertook occupational therapy and in many cases the patients became ambulatory after having previously been bedridden. It was also clinically evident that the narcotic requirements for this group of patients decreased to a marked degree. At present an attempt is being made to evaluate this observation more objectively.

Comment

The concept of using anabolic agents to increase nitrogen retention is not new or original. The metabolic changes in advanced pelvic malignancy are also familiar to most investigators. The place of a total care program in the management of advanced pelvic malignancy is significant, however. Too often these patients were relegated to custodial care in chronic disease hospitals and maintained on bed rest and increased dosage of narcotics.

The nutritional status of these patients must receive constant attention. In addition to the specific dietary formula, it is essential that the nutritionist supply a diet containing natural vitamins and minerals. It has been suggested that in this form they are more important in cellular metabolism. To insure an adequate intake of these food essentials, however, supplements are recommended. The total calorie value of the diet supplied was arrived at by trial and error taking into consideration the fact that most of the patients were elderly women leading a sedentary existence. It was felt that a diet of between 2,000 and 2,500 calories daily would supply the energy necessary for the existence of such a woman. Also the catabolic processes of this protean disease would be covered adequately by this total calorie intake.

The secondary anemia present in these patients may at times necessitate the use of blood transfusions and also the use of hematinics. Whole blood is used when the hemoglobin is below 8.0 Gm. per cent. The supplying of necessary formed proteins in this rapid manner is essential to the patient with such a severe secondary anemia.

The use of hematinics, as such, is not a routine. Rather, it is felt that with adequate nutrition, as supplied in the diet, and the restoration of normal metabolism the body can adequately handle the problem. When hematinics are used, the iron chelate form offers the advantage of high tolerance with minimal side effects.

While the anabolic effects of testosterone are well substantiated, the side effects offer many disadvantages for use in our patients. The possibility of masculinization while not as significant in this particular age group or a problem in patients with advanced cancer is still somewhat of a deterrent to the

use of testosterone. The possibility of salt and water retention limits the use of testosterone, particularly in this age group where many of the patients already have impaired cardiac function. For this reason, patients who receive testosterone propionate as the anabolic agent in management have a cardiac evaluation. This includes an electrocardiogram, venous pressure studies, and electrolyte studies. In our early experiences with testosterone therapy, 2 patients with myocardial damage went into cardiac failure. This was secondary to salt and water retention associated with testosterone therapy.

In contradistinction, Weston,[7] Goldfarb and others[6] have reported that norethandrolone when used in cardiac patients has little if any effect on sodium retention and does not increase the incidence of cardiac failure.

The changes in electrophoretic patterns are consistent with anabolism and improvement in the patient's metabolic status. Before treatment, all these patients had a marked increase in gamma globulin which is consistent with a chronic disease.[8] The reversal of this pattern has not been adequately explained as yet but the reversal of hypergammaglobulinemia may serve as an indicator of changes in protein metabolism. This may well indicate a reversal of negative nitrogen balance. With the use of anabolic agents and improvement in protein metabolism, the electrophoretic patterns showed an increase in the albumin fraction. This is consistent with protein synthesis.

Anabolic agents offer the patients a chance to form protein tissues. This includes an increase in muscle, bone matter, hemoglobin, and body tissues in general as manifested by linear growth, increased weight (not associated with fat and edema), and improved metabolic balances of tissue constituents such as nitrogen, phosphorus, sodium, and potassium.

It was interesting to note that many of the patients who were considered as radiation or surgical failures or poor risks for further therapy, after several weeks in the total care program were able to undergo either additional radiation or surgery. It was also noted that radiation sickness or injury was minimal in these patients. Recently Graham[9] has indicated that the use of anabolic agents may change the sensitivity of the tumor cell and radioresistant cells may become more radiosensitive. While we have not substantiated this observation, we do feel that the patients in positive nitrogen balance do tolerate radiation therapy to a greater degree. We in no way suggest that this total care program with correction of metabolic disturbances cured any cancer patients. We do feel that we have improved the over-all condition of the patients and removed them from therapeutic oblivion and made it possible for further specific therapy to be carried out.

Summary

1. The metabolic changes seen in advanced pelvic malignancy have been presented.

2. A total care program for these patients has been discussed with emphasis on nutritional factors and the use of anabolic agents.

3. In a small study group improvement of metabolic status followed the use of testosterone and norethandrolone. Results of this study have been analyzed.

4. The metabolic status of a cancer patient is an important factor in response to all modalities of therapy and is a significant part of a total care program.

References

1. Myers, W. P. L.: Bull. New York Acad. Med. 33: 704, 1957.
2. Stone, Martin L., and Goldfarb, Alvin F.: Bull. New York M. College. (In press.)
3. Kochakian, C. D., and Murlin, J. R.: J. Nutrition 10: 437, 1935.
4. Kenyon, A. T., Sandiford, I., Bryan, A. H., Knowlton, K., and Koch, F. C.: Endocrinology 23: 135, 1938.
5. Hershberger, L. G., Shipley, E. G., and Meyer, R. K.: Proc. Soc. Exper. Biol. & Med. 83: 175, 1953.
6. Goldfarb, A. F., Napp, E. E., Stone, M. L., Zuckerman, M. B., and Simon, J.: Obst. & Gynec. 11: 454, 1958.
7. Weston, Raymond, E.: Proceedings of a Conference on the Clinical Use of Anabolic Agents, G. D. Searle and Company, 1957, pp. 6-11.
8. Chesrow, E. J., Turner, G. C., Schaffner, F., and Musci, J.: Geriatrics 12: 642, 1957.
9. Graham, R., and Graham, J. B.: Cancer 8: 59, 1955.

DEPARTMENT OF CURRENT OPINION

Pertinent Comments

THE ADMINISTRATION OF VITAMIN K TO LABORING MOTHERS

THE clinical impression many have that hyperbilirubinemia problems in the newborn are annually increasing may not be statistically valid; nevertheless there does not seem to be any significant diminution in the frequency of neonatal jaundice. Under these circumstances it would probably be highly pertinent to comment on the administration to the mother in labor of a vitamin K analogue and the occurrence of marked hyperbilirubinemia in their infants.

There is adequate evidence in the medical literature which would convincingly indicate that the vitamin K analogues are capable of causing hyperbilirubinemia when administered in large amounts to premature infants. As yet, however, there has been no suggestion that maternally administered "K" could have the same effect on the baby.

Recently we became aware of an association between the administration of large amounts (72 mg.) of a vitamin K analogue, menadione sodium bisulfite (Hykinone), intravenously to mothers in labor and the occurrence of marked, early hyperbilirubinemia in newborn premature infants. We have encountered 7 such cases, the details of which are listed in Table I. These infants were first noted to have markedly elevated levels of serum bilirubin between 40 and 72 hours of age. All but one were treated with exchange transfusion in an effort to prevent neurologic damage (kernicterus) from the hyperbilirubinemia. Under ordinary conditions jaundice of this degree does not occur until the fourth to the sixth day of life.

Inasmuch as doses as small as 1 to 10 mg. when given by mouth to the mother have been shown to have an effect upon the prothrombin time of infants on the third day of life, the free placental transmission of vitamin K

appears to be established. With the parenteral administration of a substance of a low molecular weight such as Hykinone, the amount reaching the fetus is probably enhanced.

TABLE I

CASE	WEIGHT (GRAMS)	BLOOD GROUP		HYKINONE DOSAGE			HIGHEST BILIRUBIN (MG. %)	FOLLOW-UP
		INFANT	MOTHER	AMOUNT (MG.)	ROUTE	HOURS PRIOR TO DELIVERY		
1	1,575	O–	O–	72	I.M.	112	35	Died—kernicterus
2	2,353	O+	B+	72	I.V.	34	21	Normal at age of 1 year
3	1,680	A+	AB+	72	I.M.	10	28	Normal at age of 11 months
4	1,530	B+	B+	72	I.V.	5	26	Died at age of 1 month. Liver abscess, sepsis
5	1,431	A+	A+	72	I.V.	24	28	Normal at age of 9 months
6	2,013	A+	O+	72	I.V.	2	46	Normal at age of 6 months
7	2,792	O+	O+	72	I.V.	3	47	Retarded development

From the findings presented here, the routine intramuscular administration of appropriate doses of vitamin K analogues cannot be impugned. But because of the risk involved we feel that there are no indications for the routine administration of *large* amounts of menadione sodium bisulfite ante partum and that it is a practice which should be discontinued.

A more detailed report of this study will be published later. In the interim we would appreciate hearing from other doctors who may have made similar observations.

Jerold F. Lucey, M.D.
Robert G. Dolan, M.D.

UNIVERSITY OF VERMONT
COLLEGE OF MEDICINE, DIVISION OF PEDIATRICS
BURLINGTON, VERMONT

PECULIAR TO WOMEN

WHEN the day of complete preventive medicine finally dawns, the physician's role as the bearer of bad tidings will be considerably altered. With the well patient regularly seeking examination and advice, with perhaps medicinal and hormonal cures more readily available, the doctor will discuss with his patients Incipient Details; the need for Minor Corrective Procedures; or the happy fact that All Is Well. But until that day dawns bright and clear, his role will continue to be so much of the time the Confirmer of Worst Suspicions; the Announcer of Major Diagnoses; the Bearer of Ominous Tidings.

No one of us revels in this aspect of our occupation; each of us strives to find soothing words and easy methods for announcing the most damning diagnosis. Perhaps indeed all of us have so concentrated on what we shall say, that we have not listened attentively enough to what the patient responds.

But listen closely to what they are saying . . . .

Tell a man he has pneumonia, and he says: "Gosh, Doc, how long will it take me to get over it?" Tell a woman she has pneumonia and she says: "Now where did I possibly get that?"

He goes from the moment of diagnosis forward; she goes from the moment of diagnosis backward. He has blueprints on the drawing board, a project in his dreams; he is interested in the ultimate leaf on the final branch. She is the receiver of the seed, the harborer of implantation and early growth; her interest is in primal causes and the deep roots. It is almost impossible to announce the finding of a simple cervical polyp without entering into a discussion of where polyps come from, and why.

But listen closely to what they are saying . . . .

Tell a man he has tuberculosis and: "Some son-of-a-gun must have coughed in my face." Tell a woman she has tuberculosis and she says: "What do you suppose I did to get that?"

He is instantly sure that his environment is at fault; something outside him gave him this disease. She is apparently equally sure that something inside her was at fault, and takes the personal responsiblity for her own diseases. As male vanity makes him immune to the thought that he might be a contributor to the etiology of his diagnosis, the feminine tendency to personalize makes her an active participant in the disease process.

But listen closely to what they are saying . . . .

From the man: "Well, that's the way the ball bounces." "I suppose if the bullet has your name on it . . . ." From the woman: "But I've always been a good wife and mother, why should this . . . ." "Both my sister and my

sister-in-law played around and raised Cain, yet they've never had anything like this." "Why does this come along just when we have the children finally raised and educated?"

The early Christian conscience is best perpetuated in the female breast. Illness is a divine retribution; good health should be the reward for the Good Life. Jove sits with thunderbolts and hurls them at the badly behaved; and the thunderbolts are named Carcinoma, Sarcoma, and Tumor.

Not one of these characteristic differences in reactions can we change one iota. As we define the terms Male and Female in this society, these are innate responses, inherent in our masculinity and femininity; and not one of us is inclined to do away with the differences under these headings.

One does not seek, therefore, uniformity of response. There is no Right or Wrong to be considered; no type of reaction which is necessarily better than another type. We cannot significantly alter that which is masculine in us; that which is feminine in our patients. But one does seek to increase his sympathetic awareness of these differences; for from such awareness comes the Understanding Heart.

An interest in etiology and the first cause; a sense of personal responsibility for illness; the overtones of divine retribution . . . . Perhaps the Gynecologist sees these converge most frequently in the woman experiencing a spontaneous abortion. While he is outlining to her the future: "A little anesthesia, a curettement, a day or so in the hospital," she is discussing in her mind the past: "Where did this come from; what did I do to cause it; I've let my husband down." These thoughts need recognition, human understanding, and the appropriate discussion as an antidote.

Practicing the specialty of the Diseases Peculiar to Women should make us aware of the Responses Peculiar to Women. *Listen to what they are saying. . . .*

A. C. B.

Reviews and Abstracts

EDITED BY LOUIS M. HELLMAN, M.D.

REVIEWS OF NEW BOOKS

Anaesthesia for Nurses. By Eric Godwin. 98 pages with 12 figures. Baltimore, 1957, The Williams & Wilkins Company. $2.50.

A concise, highly readable handbook, *Anaesthesia for Nurses,* is admirably suited as a primer for the nurse in training. In fourteen chapters the field of anesthesia as it relates to general nursing is detailed in a clear and informative manner. The chapters on "Pre-operative Management," and "Post-operative Care: Complications," are particularly good. Not only the nurse in training but the graduate will find the brief but concise chapter on pharmacology worth while, for it brings together the drug armamentarium of the anesthetist which is pertinent.

It should be emphasized that the small volume is directed toward nurses in general. Its value for the nurse anesthetist would be markedly limited. For the audience for whom it was written it can be highly recommended. The photographs, while very good, show British apparatus generally little used in the United States.

Aortography: Its Application in Urological and Some Other Conditions. By W. Barr Stirling. 292 pages with 155 figures. Baltimore, 1957, The Williams & Wilkins Company. $10.00.

Despite the well-established place that aortography and contrast arteriography have achieved in the management of many surgical and urological problems, there is still a great reluctance by many surgeons to make use of these valuable diagnostic aids. This stems partly from the fear of serious complications arising from these procedures and partly from a belief that elaborate equipment is necessary, neither of which is necessarily true.

This monograph written by a urological surgeon, based upon a personal experience with some 500 aortograms, will do much to convince the medical profession of the practical utility and relative safety of this method of examination. In the author's personal series of 500 cases in which the aorta was punctured, no fatality, no appreciable morbidity, or serious complication was encountered. This is in contrast to the experience of others, indicating that the procedure is not without risk but this can, in indicated cases, be minimized by elimination of faulty technique.

The major hazards and complications encountered are taken up individually in a separate chapter and suggestive comments made for their correction. Radiation exposure to the patient is not mentioned and the danger of exposure to the operator is only briefly

considered. Age, hypertension, and arteriosclerosis do not preclude translumbar aortography apart from anesthetic consideration. The only major deterrents are severe renal disease and iodide sensitivity.

The disturbances caused by the introduction of 20 ml. of fluid directly into the aorta with an injector under pressures of 800 mm./Hg at no time produced a rise in intra-aortic pressure greater than 10 mm./Hg and at no time transmitted a rise of more than 5 mm./Hg to the renal arteries. This rise in pressure is insignificant and less than that which occurs physiologically during stress or emotion. Emphasis is chiefly and almost exclusively on urological conditions although a few other disorders are included. The text is beautifully and substantially illustrated with about 138 clear, full-page reproductions of x-ray plates (about 155 illustrations in all) supplemented with brief case histories and operative findings where available.

The Biologic Basis of Cancer Management. By Freddy Homburger. 354 pages, 39 tables, 10 figures. New York, 1957, Paul B. Hoeber, Inc. $10.00.

Most of the volumes that have been written in the field of cancer have been concerned with the narrow interests of the author. Thus, we have seen books related to a consideration of pathology, surgical therapy, or other specific areas. In the *Biologic Basis of Cancer Management,* Dr. Homburger, an internist by background, has endeavored to correlate basic and clinical research for the enhancement of progress in both. He has digested the vast amount of evidence being accumulated in the literature on the occupational and environmental causes of cancer, experimental carcinogenesis, role of heredity, role of viruses and hormones. A concise but excellent presentation on the host and tumor interrelations in human beings and animals is a high light of the discussion of the biologic behavior of cancer.

In the light of recent enthusiasm for and interest in the role of chemotherapy, the chapter on the chemistry of tumors is particularly apropos and interesting since the author subsequently presents a section on the principle of chemotherapy. The latter concerns itself primarily with the clinically employed agents rather than the myriad of agents under investigation in the field of experimental cancer. Rather than going into specific techniques and details, the author wisely discusses principles of radiotherapy and surgical therapy in cancer. He closes his book with a very appropriate statement that "while we are laboring on the experimental and theoretical level we must at the same time make every effort on the practical level to use all the knowledge we have for cancer prevention, and to develop ways and means for the earlier discovery and diagnosis of those cancers known to be curable by present-day techniques." All in all, this reader enjoyed Dr. Homburger's refreshing and informative contribution to cancer literature.

Human Cancer. By Maurice M. Black and Francis D. Speer. 273 pages, 34 figures, 15 tables. Chicago, 1957, The Year Book Publishers, Inc. $7.50.

In their preface, the authors state that a "concise and systematic presentation of the subject (human cancer) may serve to guide the neophyte to what is known, indicate the unknown and controversial, and, perhaps most important of all, orient him toward critical observations and the contribution of new knowledge." Indeed, this is a commendable and desirable thought. However, the authors of *Human Cancer* have sacrificed a tremendous amount of valuable and significant information for the sake of conciseness. The book is very superficial in the presentation of not only the factual knowledge of the various types of malignancy but also the important areas of cancer control. The opportunity to convey an understanding of cancer control with an adequate text and ample illustrations is missed. The reader interested in learning something about cancer completes the book with the feeling that he has read a series of scientific journals by the title of the articles therein.

Human Infertility. By C. Lee Buxton and Anna L. Southam. 229 pages, 43 figures, 25 tables. New York, 1958, Paul B. Hoeber, Inc. $7.50.

Drs. Buxton and Southam have undertaken a penetrating analysis of the value of the current tests for human infertility.

The clinical material presented consisted of 1,568 infertile couples followed for one to 10 years. As a standard for future comparison 37.5 per cent of the women had a pregnancy. Of these, 23.5 per cent became pregnant within one year of the initial interview. The study of the infertile couple by an organized plan began in 1943. The diagnostic methods have not changed significantly but there has been alteration in the interpretation of the results. The real message of the book is the analysis of results of therapy.

The authors present their facts with the skill of trained investigators. Some details inspire criticism, especially in the section on the treatment of ovarian imbalance. Although significance tests are applied the groups analyzed are not comparable.

A minor criticism is the misuse of the term, biopsy, which is the name of an examination and not the name of tissue or a specimen taken for examination. On page 80 the authors refer to a 10 day endometrium. To this reviewer's knowledge preovular endometria are not datable.

The references are meager for a publication of such good quality.

Many case reports are cited in detail to illustrate the management and study of individual infertility problems. The technique is a good method for instruction.

The book is recommended as a reference for the current thoughts on and value of the diagnostic techniques utilized in the investigation of the infertile couple.

The Illustrated Birth Control Manual. By Valeria Hopkins Parker. 392 pages with 178 illustrations. New York, 1957, Cadillac Publishing Co. $5.00.

As the subject of birth control comes to be more openly discussed and a part of modern living, the need for dissemination of accurate scientific information to the laity in a simple, readily comprehensible, nontechnical manner is apparent. A measure of success is achieved by the author, who strives to do this in 392 pages with an overly generous, though at times repetitive, supply of illustrations, 178 in all, including 27 color plates.

The first half of the book is concerned with the anatomy of the male and female reproductive organs and the sex act. Following this, the types of birth control methods are briefly presented, the recommended as well as the harmful or useless and outmoded means. The diaphragm jelly, the condom, and the rhythm methods, i.e., the most popular and most frequently used of the recommended methods, are given more space and discussed in separate chapters. A directory of birth contol and infertility services in the United States and Canada has been appended.

The book is clearly directed toward a nonprofessional level and may find its greatest value as professionally prescribed reading for lay persons.

BOOKS RECEIVED FOR REVIEW

L'Année endocrinologique. By M. Albeaux-Fernet, L. Bellot, P. Bugard, J. Chabot, J. Deribreux, M. Gelinet, and J. D. Romani. 240 pages with 19 figures. Paris, 1958, Masson & Cie. 2,000 fr.

The Endocrinology of Reproduction. Edited by Joseph Thomas Velardo. 340 pages, 191 figures, 18 tables, 1 plate. New York, 1958, Oxford University Press. $15.00.

Pathophysiology in Surgery. By James D. Hardy. 704 pages, 278 figures, 18 tables. Baltimore, 1958, The Williams & Wilkins Company. $19.00.

Le Placenta humain—Aspects morphologiques et fonctionnels. By Professor Jean Snoeck. 720 pages, 175 figures, 48 tables. Paris, 1958, Masson & Cie. $25.00.

Reproductive Physiology. By A. V. Nalbandov. 271 pages, 38 figures, 56 tables. San Francisco, 1958, W. H. Freeman & Company. $6.75.

Les Troubles de la puberté féminine et leurs traitements. By J. E. Marcel, Pres., Société française de gynécologie. 366 pages, 43 figures, 20 tables. Paris, 1958, Masson & Cie. 3,800 fr.

SELECTED ABSTRACTS

Canadian Medical Association Journal

Vol. 78, May 1, 1958.

Hurtig, A.: Occult Uterine Bleeding: A Daily Record of 254 Cycles, p. 681.

A reliable practical method of daily testing for uterine occult bleeding has been used through 254 cycles on 80 apparently healthy women. Occult intermenstrual bleeding was defined as occult bleeding occurring without the patient's knowledge at least 24 hours after visible blood has disappeared postmenstrually and 24 hours before onset of the next menses.

Each morning on arising, the patient inserted a vaginal tampon, removed it after 30 minutes, and dropped it into a specially made polyethylene envelope. Four drops of distilled water were dropped on the tampon and two minutes later, the tampon tip was then firmly touched to two pieces of filter paper. The filter paper was tested for pH and then occult blood using Hematest and Occultest for concentrations of hemoglobin of 1 in 10,000 and 1 in 100,000, respectively.

A sharply defined episode of occult intermenstrual vaginal bleeding was found in 118 cycles. Twenty-four cycles in 8 women with a long-standing history of sterility did not show one single positive test. In 74 cycles occult bleeding at 1/10,000 occurred only on one day during the entire intermenstrual period.

Intermenstrual occult blood related to ovulation apparently appears at the cervix a few hours after ovulation if the tubes are open, and apparently comes from the ovary. Two patients with radiologically proved closed tubes, secretory endometrium, and sterility had not one single positive test. The author entertained the possibility that the second distinct episode of occult bleeding is from a second ovulation in the same cycle.

The finding of a persistent positive pattern should lead to the discovery of early ulcerative lesions of both a benign and a malignant nature. This finding should always precede frank abnormal bleeding for varying periods.

The continuous occult bleeding found in all of the 9 cases of pregnancy coincides with the expected time of implantation of the trophoblast. Perhaps this continued occult blood loss is a factor in the cause of some anemia in pregnancy.

JOHN J. DETTLING

Vol. 78, June 15, 1958.

Roberts, M. E.: Tetanus Neonatorum, p. 922.

Six cases of neonatal tetanus are reported which occurred in home deliveries from a rural Negro community. The infants were brought into the hospital between the sixth and fifteenth days after birth with clinical signs consisting of generalized convulsions, opisthotonic spasms, stiffness of the arms and legs, spasm of the jaw, and boardlike abdomen.

The incidence is higher in the Negro population than in the white.

The cerebrospinal fluid shows a rise in protein with little or no increase in cell count. In no case was the diagnosis of tetanus confirmed by culture of *Clostridium tetani* from the umbilicus. There was no evidence of septicemia in any case.

Tetanus antitoxin was given intravenously in all cases at the earliest opportunity and supplementary doses either intravenously or intramuscularly. Phenobarbital, paraldehyde, and Pentothal were used as sedatives. The author discusses the place of chlorpromazine in relation to the other sedatives.

The prognosis is depressing. Only one infant survived. Tetanus neonatorum is a disease which should not occur in communities where a high standard of hygiene and nursing care for the newborn is claimed.

JOHN J. DETTLING

Journal of Clinical Endocrinology and Metabolism

Vol. 18, July, 1958.

Dunn, John T., and Stanbury, John B.: Metabolism of Triiodothyronine in Man, p. 713.

The authors administered intravenously to 10 euthyroid patients I^{131} labeled 3:3′:5′-triiodothyronine to determine its disappearance from the serum and accumulation in the urine. The substance was rapidly degraded and its iodide appeared as free iodide in the serum. Within 24 hours, more than 50 per cent of the administered labeled iodine was usually eliminated in the urine, most of it as free iodide. Since the metabolic degradation of 3:3′:5′-triiodothyronine is so rapid, it is improbable that it is a naturally occurring thyroid hormone in man.

J. EDWARD HALL

Vol. 18, August, 1958.

Albert, A., Kelly, Shirley, and Kobi, Joan: Human Pituitary Gonadotropin From Urine of Normal Men, and Postmenopausal and Castrated Women, p. 843.

There is a difference of opinion as to whether or not human urine contains two gonadotropic hormones or one gonadotropic hormone possessing the activity of both FSH and LH in consistent proportion. The authors tested for the HPG in urine from men and postmenopausal and castrated women. The assay system employed was the simultaneous response of the ovary and uterus of the immature rat. It was found that the parameters for HPG prepared from the urine of males and of postmenopausal and castrated women by the same process did not differ.

The present data serve to characterize one human gonadotropic material.

J. EDWARD HALL

Borglin, N. E.: Serum Transaminase Activity in Uncomplicated and Complicated Pregnancy and in Newborns, p. 872.

Glutamic-oxalacetic transaminase activity was determined in serum from pregnant women with and without complications (missed abortion, incomplete, complete, and threatened abortion, hepatosis, and toxemia) and from newborn infants (umbilical cord blood). The activity was found to be normal in uncomplicated pregnancy, at delivery, in the puerperium, and in different types of abortion, but to be somewhat increased in hepatosis. In toxemia the activity was often markedly increased (30 per cent) but returned to the normal level as the symptoms of toxemia disappeared. This increase in the transaminase activity is possibly due to liver damage.

J. EDWARD HALL

Borglin, N. E.: Serum Transaminase Activity and Vitamin B_6 in Pregnancy, p. 878.

Glutamic-oxalacetic transaminase in serum was determined toward the end of pregnancy. The determinations were made before and after incubation of the serum with pyridoxine orally for a fairly long time. Neither medication with pyridoxine nor incubation of the serum with pyridoxal phosphate produced an increase in transaminase activity. Thus, judging by the activity of glutamic-oxalacetic transaminase in serum, under the conditions of the study, pregnancy is not accompanied by a deficiency of vitamin B_6.

J. EDWARD HALL

The Lancet

Vol. 1, June 21, 1958.

Anderson, W. J. R., Baird, D., and Thomson, A. M.: Epidemiology of Stillbirths and Infant Deaths Due to Congenital Malformation, p. 1304.

Among 37,585 single births that occurred in the Aberdeen Maternity Hospital between 1938 and 1955, there were 237 stillbirths and infant deaths due to congenital malformation (6.3 per 1,000 births). Of these 60 were due to anencephalus (1.6 per 1,000 births), 88 to other deformities of the central nervous system (2.3 per 1,000 births) and 89 (2.4 per 1,000 births) to other malformations. On the basis of 20,961 that occurred in the city of Aberdeen these rates were 1.5, 1.8, and 2.2, respectively. In Scotland as a whole during the years 1939 to 1955 the incidence of anencephalus was 2.7 per 1,000 births, of malformation of the central nervous system 3.7, and of other malformations 3.9 per 1,000 births.

In the Aberdeen Maternity Hospital group anencephalus and other abnormalities of the central nervous system were much more common in the offspring of the younger primiparas, whereas deaths due to other malformations were more common among those mothers aged 35 or more. Mongolism accounts for the latter observation.

In 8,221 married primiparas delivered in Aberdeen between 1949 and 1955 the incidence of anencephalus varied with the social class to which the woman belonged, being highest among those in the lower social classes. The same was true to a lesser degree of the incidence of other abnormalities of the central nervous system but the incidence of other abnormalities did correlate with the social class to which the woman belonged. In Scotland as a whole the incidence of stillbirths due to congenital malformations varied from region to region being highest in the industrial regions in the central and southern areas and lowest in the Crofting Counties of the Northwest. The incidence of anencephalic stillbirths in Aberdeen was 1.7 per 1,000 births, in Edinburgh 2.5, in Dundee 2.9, and in Glasgow 3.1 per 1,000 births.

These data are interpreted as suggesting that primigravidas living in poor social circumstances have a higher risk of producing an anencephalic fetus. The inference is not made, however, that environmental influences are necessarily the major cause of malformations of the central nervous system. Such influences may merely bring out latent genetic

tendencies. Also, whatever the influence of poor environment, it may have been effective before as well as during pregnancy. Prevention is likely to depend on long-term measures that will secure high standards of growth and health of the prospective mother.

DAVID M. KYDD

Vol. 2, July 26, 1958.

Gunz, F. W., Borthwick, R. A., and Rosseston, G. L.: Acute Leukemia in an Infant Following Excessive Intrauterine Irradiation, p. 190.

A baby who was admitted to the Christchurch, New Zealand, Hospital at the age of 10 months was found to have acute granulocytic leukemia. Staphylococcal septicemia developed and the baby died 11 days later. The patient's mother was an exceptionally obese woman (238 pounds). Because of this there was doubt about the position of the fetus and 3 x-ray examinations (5 exposures) were undertaken during the last month of the pregnancy. The fetus initially lay as a breech and then transversely. After an external version, surgical induction was performed. The labor was quick and uncomplicated. The infant weighed 9 pounds, 12 ounces at birth and appeared to be normal during the first 9 months of life.

Subsequently calculations were made of the fetal exposure resulting from the 3 anteroposterior and 2 left-to-right lateral x-ray examinations of the obese mother. The total dose to the center of the fetus amounted to 25.3 r, to the center of the skull, 57.3 r, and to the mean center of the fetal tibias, 26.6 r. Thus it is possible with standard techniques and only those exposures which are regarded as essential for the safe conduct of a difficult obstetrical case to administer much higher doses than the average dose given to pregnant women that has been estimated by Rabinovich (Lancet 2: 1261, 1956) to be 1-2.5 r. The amount of radiation received by this fetus approximated the probable amount received by survivors in Hiroshima and Nagasaki 1,500-2,000 M. from the hypocenter. The incidence of leukemia among these people was 200-300 per cent compared with that of survivors more than 2,000 M. from the hypocenter.

The latent period in this baby was much shorter than that reported for adults known to have been exposed to radiation but the youth of this patient does not allow comparison. The occurrence of leukemia in this infant may have been happenstance, but the difficulties encountered in examining this very large woman led to a modification of the technique for obstetrical x-ray exposure so that the dose to the center of the fetus was reduced to 1.9 r when a woman of this size is dealt with and much less with a woman of average size.

DAVID M. KYDD

Metabolism

Vol. 7, September, 1958.

Chesley, L. C., Valenti, C., and Rein, H.: Excretion of Sodium Loads by Nonpregnant and Pregnant Normal, Hypertensive and Pre-eclamptic Women, p. 575.

The renal excretion of sodium was studied in 53 women, before, during, and after the rapid infusion of 24 Gm. of sodium chloride in 3 per cent solution. Concurrent measurements of the inulin clearance were made, in order to calculate the quantities of sodium filtered by the glomeruli and reabsorbed by the tubules.

Both pregnant hypertensive and pre-eclamptic women differed from normal in that sodium excretion did not increase with augmented rates of sodium filtration at the glomeruli. At any given filtered load of sodium, tubular reabsorption was greater in women with pre-eclampsia than in the normal subjects. It was concluded that the salt retention of pre-eclampsia cannot be explained upon the basis of the reduction in glomerular filtration rate alone, although this is probably an important factor. The marked alteration in renal tubular function also seems to play a role.

LEON C. CHESLEY

Münchener Medizinische Wochenschrift

Vol. 100, May 30, 1958.

*Bauer, O.: Puerperal Fever—Then and Now (Part I), p. 865.
*Besold, F.: The Treatment of Placenta Previa—Today, p. 869.

Vol. 100, June 6, 1958.

*Bauer, O.: Puerperal Fever—Then and Now (Conclusion), p. 901.

Vol. 100, June 13, 1958.

Schall, L.: Vitamin K and Kernicterus in Prematures, p. 932.

It is shown that high dosage of vitamin K to premature babies increases the incidence of kernicterus. In the past, it was routine to give prematures 10 mg. of synthetic vitamin K three times daily for 3 days. Of 442 such babies, 53 had kernicterus at autopsy. In 176 premature babies who received only 1 mg. three times daily for 3 days, no kernicterus was seen.

It is, therefore, concluded that only small amounts of vitamin K should be used.

WALTER F. TAUBER

New England Journal of Medicine

Vol. 259, September 18, 1958.

Ingalls, Theodore H., and Philbrook, F. Randolf: Monstrosities Induced by Hypoxia, p. 558.

The authors report on a series of experiments designed to test the hypothesis that hypoxia may be a teratogenic agent for the embryo as it is for the fetus; to examine the theory that monstrosities are acquired malformations of the embryo which bear some analogy to acquired anomalies of the older fetus; to observe the occurrence and meaning of gradations of defect and associated malformations; and to test whether multiple environmental stresses such as hypoxia and hypothermia can enhance one another's teratogenic impact on the embryo. An indirect approach to this problem was devised with the use of fish embryos, which permit direct visualization of the embryos subjected to stress, as well as of deformities produced thereby. The most suitable fish for the experiments was found to be the zebra fish *(Brachydanio rerio);* in the summer months, when the ecologic problems of maintaining the stock colony were greatest, *Fundulus heteroclitus* was used. Batches of fertilized eggs of *Brachydanio rerio* were subjected to hypoxia in a flask containing aquarium water rendered oxygen poor. Subsequently, embryos were examined under the dissecting microscope at about the time of hatching. It was found that temperature fluctuations play an important part in determining maldevelopments of the embryo. Extreme conditions of deprivation were necessary, however, to produce bizarre anomalies representing departures from the normal sequence of growth. The various abnormalities which could be produced by these methods included anophthalmia, microphthalmia, cyclopia, rumplessness, hydropericardium, and conjoined twins. In discussing their results, the authors remark that in published observations made on the effects of rubella and the Hiroshima explosion on pregnancy in human beings, anomalies were frequently observed after maternal illnesses in the second, third, and fourth months, but there has been a paucity of observations indicating a teratogenic impact during the first month of pregnancy. The assumptions are either that death of the embryo and abortion were the usual consequences of maternal rubella or bomb injury in very early pregnancy, or that the embryos survived unscathed. Cases have been observed in the experimental animal in which maternal hypoxia can be shown to produce congenital defects after implantation of the conceptus at about the eighth or ninth day of gestation. Malformations are occasionally, though seldom, observed in fetuses subjected to the same maternal

*This article has not been abstracted.

stresses in the amphibious stage of their existence. The authors add to the information on this subject by reporting that successful experiments indicate clearly that a predictable sequence of deformities can be produced in the zebra fish by critical hypoxic stress, and that the nature of the malformation produced depends upon the time of the metabolic interference. The greater the hypoxic stress, the higher the fatality rate and the greater the probability of occurrence of so-called "monstrous" defects (anophthalmia, microphthalmia, cyclopia, etc.). In the experiments reported, the critical stage for the occurrence of anophthalmia and microphthalmia was 2 to 8± cells; for cyclopia it was the 16 to 32± cell stage; while for rumplessness, the morula, for hydroceles, the blastula, and for conjoined twins, the gastrula stages of embryonic existence were the crucial ones. Discussions and illustrations of the vistas opened by these experimental observations include special reference to the phenomenon of ectromelia, but the authors are frank to state that the broad problem needs to be studied in the field in the search for environmental factors which may affect embryonic development adversely.

DOUGLAS M. HAYNES

Proceedings of the Society for Experimental Biology and Medicine

Vol. 98, July, 1958.

Weld, J. T., and Kean, B. H.: A Factor in Serum of Human Beings and Animals That Destroys *T. vaginalis*, p. 494.

Pure cultures of Trichomonas were injected into rabbits. Blood and organ cultures taken 10 to 15 minutes later were sterile. Fresh sera from human subjects, guinea pigs, rats, hamsters, dogs, and rabbits kill and destroy *T. vaginalis*. Heating serum to 56° C. for 30 minutes abolishes this property.

LEON C. CHESLEY

Kolin, A., Herrold, G., and Assali, N.: Electromagnetic Blood Flow Meter Yielding a Base Line Without Interruption of Flow, p. 550.

The flow meter has been improved so as to permit continuous recordings of blood flow while the test animal is moving about. Also, the base line for zero flow can be recorded by merely turning off the magnet, rather than by interrupting the flow in the blood vessel as was necessary in earlier forms of the flow meter.

LEON C. CHESLEY

Seltzer, H. S., and Clark, D. A.: Evidence for Conversion of Corticosterone to Aldosterone in Man, p. 674.

Excretion of aldosterone at least doubled in 3 men who were infused with 200 to 300 mg. of corticosterone. This suggests that the corticosterone was oxygenated to aldosterone, but much more work must be done to evaluate this hypothesis.

LEON C. CHESLEY

Items

American Board of Obstetrics and Gynecology

The next scheduled examinations (Part II), oral and clinical, for all candidates will be conducted at the Edgewater Beach Hotel, Chicago, Illinois, by the entire Board from May 8 through 19, 1959. Formal notice of the exact time of each candidate's examination will be sent him in advance of the examination dates.

Candidates who participated in the Part I examinations will be notified of their eligibility for the Part II examinations as soon as possible.

Current Bulletins of the American Board of Obstetrics and Gynecology, outlining the requirements for application, may be obtained by writing to the Secretary:

ROBERT L. FAULKNER, M.D.
2105 ADELBERT ROAD
CLEVELAND 6, OHIO

Establishment of Multiple Birth Roster

The New York City Department of Health has established a Multiple Birth Roster which is intended to be a source of information for research workers in genetics, child development, and related fields.

All multiple births involving at least two live infants are included in the Roster. The identifying, demographic, and pregnancy information available on the birth certificate of each infant will be punched on a tabulating card.

Applications for use of the Roster will be reviewed as to the qualifications of the investigator and the value of the proposed study, and investigators will be expected to adhere to such requirements as the Department may deem necessary.

Requests should be submitted formally to

DR. HAROLD JACOBZINER
ASSISTANT COMMISSIONER FOR MATERNAL AND CHILD HEALTH SERVICES
NEW YORK CITY DEPARTMENT OF HEALTH
125 WORTH STREET, NEW YORK 13, N. Y.

Conference on "The Vagina"

The New York Academy of Sciences is sponsoring a conference on "The Vagina" on April 10 and 11, 1959, 9 A.M. to 5 P.M., at the Barbizon Plaza, New York City. Interested physicians, if not members of the Academy, should write to the Executive Director of the Academy, 2 East 63rd Street, for programs which will serve as tickets of admission. There is no registration fee.

WARREN R. LANG, M.D., CONFERENCE CHAIRMAN
JEFFERSON MEDICAL COLLEGE
PHILADELPHIA 7, PENNSYLVANIA

ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES*

(Appears in January and July)

American College of Obstetricians and Gynecologists. (1951) *President,* R. Glenn Craig. *Secretary,* John C. Ullery, Starling-Loving Bldg., The Ohio State University, Columbus, Ohio. Next meeting, Atlantic City, N. J., April 6, 7, and 8, 1959.

American Gynecological Society. (1876) *President,* Lewis C. Scheffey, Philadelphia, Pa. *Secretary,* Andrew A. Marchetti, Georgetown University Hospital, Washington 7, D. C. Annual meeting, May 21, 22, and 23, 1959, The Homestead, Hot Springs, Va.

American Association of Obstetricians and Gynecologists. (1888) *President,* Joe V. Meigs, Boston, Mass. *Secretary,* E. Stewart Taylor, 4200 E. Ninth Ave., Denver 20, Colo. Annual meeting, Sept. 10-12, 1959.

Central Association of Obstetricians and Gynecologists. (1929) *President,* Axel N. Arneson, St. Louis, Mo. *Secretary,* Edwin J. DeCosta, 104 S. Michigan Ave., Chicago 3, Ill. Annual meeting, The Drake Hotel, Chicago, Ill., Sept. 24-26, 1959.

South Atlantic Association of Obstetricians and Gynecologists. (1938) *President,* Charles J. Collins. *Secretary,* W. Norman Thornton, Jr., University of Virginia Hospital, Charlottesville, Va. Next meeting, Roanoke, Va., Feb. 4-7, 1959.

A. M. A. Section on Obstetrics and Gynecology. (1859) *Chairman,* Nicholson J. Eastman, Baltimore, Md. *Secretary,* Keith P. Russell, 511 S. Bonnie Brae St., Los Angeles 57, Calif. Next meeting, Atlantic City, N. J., June 8-12, 1959 (Centennial Meeting of Section).

Society of Obstetricians and Gynaecologists of Canada. (1944) *President,* J. S. Henry, Montreal, Quebec. *Secretary,* F. P. McInnis, 280 Bloor St. W., Toronto 5, Ont. Annual meeting, Mont Tremblant Lodge, Mont Tremblant, Quebec, Sept. 10-13, 1959.

American Board of Obstetrics and Gynecology, Inc. (1930) *President,* F. Bayard Carter. *Secretary,* Robert L. Faulkner, 2105 Adelbert Rd., Cleveland 6, Ohio.

Akron Obstetrical and Gynecological Society. (1946) *President,* B. N. Riddle. *Secretary,* Louis M. Walker, 1108 Second National Bldg., Akron 8, Ohio. Meetings, quarterly.

Alabama Association of Obstetricians and Gynecologists. (1940) *President,* Julian P. Hardy. *Secretary,* Lyman Findley, 819 Fourth Ave., Tuscaloosa, Ala. Next meeting, Birmingham, Ala., April 15, 1959.

Alameda County Gynecological Society. (1951) *President,* Emery P. Page. *Secretary,* Clifford Chappell, 2636 Telegraph Ave., Berkeley, Calif. Meetings, fourth Wednesday, September through June.

Arkansas Obstetrical and Gynecological Society. (1953) *President,* Charles Henry. *Secretary,* J. O. Porter. Meetings, April and October.

Atlanta Obstetrical and Gynecological Society. (1954) *President,* George A. Williams. *Secretary,* William H. Grimes, Jr., 272 Boulevard, N. E., Atlanta 12, Ga. Meetings, February, April, June, and October.

Birmingham Obstetrical and Gynecological Society. (1949) *President,* Ernest B. Oliver. *Secretary,* Eugene Howe, 920 S. 19th St., Birmingham 5, Ala. Meetings, last Thursday in January and March.

Boston, Obstetrical Society of. (1861) *President,* Alfred L. Potter. *Secretary,* A. Gordon Gauld, 1180 Beacon St., Brookline 46, Mass. Meetings, third Monday, January, February, March, April, October, and November.

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*Changes, omissions, and corrections must be received by the publisher two months in advance, by May 1 for the July Roster and by November 1 for the January Roster. Please address The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, Mo. The number after the Society's name is the year of founding. For further information, address the respective secretaries.

Bronx Gynecological and Obstetrical Society. (1924) *President,* Bernard Lapan. *Secretary,* Sidney S. Steckel, 800 Grand Concourse, Bronx 51, N. Y. Meetings, fourth Monday, October, November, January, February, March, and April.

Brooklyn Gynecological Society, Inc. (1890) *President,* Leslie Hughes Tisdall. *Secretary,* Warren A. Lapp, 731 E. 22nd St., Brooklyn 10, N. Y. Meetings, third Wednesday, October, November, January, February, March, April, and May.

Buffalo Obstetrical and Gynecological Society. (1946) *President,* Louis G. Trippe. *Secretary,* Richard W. Baetz, 216 Summer St., Buffalo 22, N. Y. Meetings, first Tuesday of each month.

Central New York Association of Gynecologists and Obstetricians. (1938) *President,* Eugene R. Duggan. *Secretary,* James N. Capps, 325 University Ave., Syracuse, N. Y. Meetings, third Tuesday, September through May.

Chicago Gynecological Society. (1878) *President,* H. Close Hesseltine. *Secretary,* William G. Cummings, 636 Church St., Evanston, Ill. Meetings, third Friday, October through June.

Cincinnati Obstetrical and Gynecological Society. (1876) *President,* Lester J. Bossert. *Secretary,* John M. Glenn, 3180 Harrison Ave., Cincinnati 11, Ohio. Meetings, third Thursday, September through June.

Cleveland Society of Obstetrics and Gynecology. (1947) *President,* Edwin D. Richards. *Secretary,* Richard Glove, 3550 Warrensville Center Rd., Shaker Heights 22, Ohio. Meetings, fourth Monday, September, November, January, March, and May.

Columbus Obstetric-Gynecologic Society. (1944) *President,* Robert Inglis. *Secretary,* Ben Jacoby, 9 Buttles, Columbus, Ohio. Meetings, last Wednesday of month, September through May, except December.

Connecticut Society of American Board Obstetricians and Gynecologists, Inc. (1952) *President,* Louis F. Middlebrook, Jr. *Secretary,* Joseph Klein, 435 Farmington Ave., Hartford 5, Conn. Meetings, April and November.

Dallas-Fort Worth Obstetric and Gynecologic Society. (1948) *President,* Herman I. Kantor. *Secretary,* James T. Downs, III, 3707 Gaston Ave., Dallas 10, Texas. Meetings, spring and fall.

Dayton Obstetrical and Gynecological Society. (1937) *President,* F. G. Barr, Jr. *Secretary,* Zelique Katz, 627 Salem Ave., Dayton, Ohio. Meetings, third Wednesday each month, Van Cleve Hotel.

Denver Gynecological and Obstetrical Society. (1942) *President,* Gerard Del Junco. *Secretary,* Alvin J. Frosh, 2222 East 18th Ave., Denver, Colo. Meetings, first Monday of every month, October through May, inclusive.

Florida Obstetric and Gynecologic Society. (1948) *President,* J. W. Douglas, Pensacola, Fla. *Secretary,* T. Bert Fletcher, Jr., 1203 Miccosukee Rd., Tallahassee, Fla. Meetings, May and December.

Georgia State Obstetrical and Gynecological Society. (1951) *President,* Eugene Griffin. *Secretary,* Bothwell Traylor, 419 S. Milledge Ave., Athens, Ga. Annual meeting with Medical Association of Georgia. Interim meeting in fall.

Harris, John Warton, Obstetrical Society. (1953) *President,* William V. Luetke. *Joint Secretaries,* Madeline Thornton and William Keikhofer, State of Wisconsin General Hospital, 1300 University Ave., Madison, Wis. Annual meeting in May.

Honolulu Obstetrical and Gynecological Society. (1947) *President,* Edward Matsuoka. *Secretary,* John Ohtani, Rm. 410, Professional Center Bldg., 1481 S. King St., Honolulu, Hawaii. Meetings, third Monday of each month.

Houston Gynecological and Obstetrical Society. *President,* Arthur M. Faris. *Secretary,* William R. Knight, III, 724 Hermann Professional Bldg., Houston 25, Texas. Meetings by announcement.

Indiana Obstetrical and Gynecological Society. (1947) *President,* Mahlon Miller. *Secretary,* John E. Mackey, 3400 N. Meridian St., Indianapolis, Ind. Meetings, second Wednesday, October, January, and April.

Interurban Obstetrical and Gynecological Society. (1949) *President,* Arthur J. Wallingford, Albany, N. Y. *Secretary,* E. R. Duggan, 16 N. Goodman St., Rochester 7, N. Y. Meeting, October, 1959.

Iowa Obstetrical and Gynecological Society. *President,* Addison Brown, Des Moines, Iowa. *Secretary,* W. B. Goddard, University Hospitals, Iowa City, Iowa. Meetings, April and November.

Kansas City Gynecological Society. (1922) *President,* Floyd C. Atwell. *Secretary,* Kenneth S. Nicolay, 4635 Wyandotte St., Kansas City 12, Mo. Meetings, September, November, January, March, and May.

Kentucky Obstetrical and Gynecological Society. (1947) *President,* Joseph Liebman, Frankfort, Ky. *Secretary,* Ed. Masters, 107 Fairmeade Rd., Louisville, Ky. Annual meeting in April.

Long Beach Obstetrical and Gynecological Society. (1954) *President,* Mary F. Callaghan. *Secretary,* Philip B. Hartley, 2491 Pacific Ave., Long Beach, Calif. Meetings, quarterly.

Los Angeles Obstetrical and Gynecological Society. (1914) *President,* Alphonsus M. McCarthy. *Secretary,* John L. Gaspar, 16100 Ventura Blvd., Encino, Calif. Meetings, second Tuesday, September, November, January, March, and May.

Louisville Obstetrical and Gynecological Society. *President,* V. E. Masters, St. Matthews, Ky. *Secretary,* John Petry, Bardstown Road, Fern Creek, Ky. Meetings, fourth Monday, September, October, November, January, February, March, April and May.

Madison Obstetrical and Gynecological Society. (1950) *President and Secretary,* Donald O. Price, 1922 University Ave., Madison, Wis. Meetings, first Tuesday each month, October through June.

Maryland, Obstetrical and Gynecological Society of. (1929) *President,* A. Adler Sondheimer. *Secretary,* D. Frank Kaltreider, University Hospital, Lockwood and Greene Sts., Baltimore, Md.

Memphis Obstetrical and Gynecological Society. (1950) *President,* Walter A. Ruch. *Secretary,* Robert M. Ruch, 509B Baptist Medical Bldg., 20 S. Dudley, Memphis, Tenn. Meetings, second Tuesday, October through May.

Miami Obstetrical and Gynecological Society. (1946) *President,* Harry Kraff. *Secretary,* Norman McLeod, 249 Sevilla Ave., Coral Gables, Fla. Meetings, second Thursday, January, March, May, and November.

Michigan Society of Obstetricians and Gynecologists. (1924) *President,* James H. Beaton. *Secretary,* Robert G. Swanson, 936 Alter Rd., Detroit 15, Mich. Meetings, first Tuesday, October, December, February, April, and May.

Milwaukee Gynecological Society. (1951) *President,* Carlton Wirthwein. *Secretary,* John Thoma, 411 E. Mason St., Milwaukee 2, Wis. Meetings, fourth Monday, January, March, May, and November.

Minneapolis Obstetrical and Gynecological Society. (1955) *President,* Harold R. Leland. *Secretary,* Richard R. Fliehr, 301 Doctors Bldg., Minneapolis 2, Minn. Four meetings a year.

Minnesota Obstetrical and Gynecological Society. *President,* John L. McKelvey. *Secretary,* Edward A. Banner, 200 First St., S. W., Rochester, Minn. Meetings, spring and fall.

Mississippi Obstetrical and Gynecological Society. (1947) *President,* K. Ramsey O'Neal, Hattiesburg, Miss. *Secretary,* Blanche Lockard, 838 Lakeland Drive, Jackson, Miss. Meetings, spring and fall.

Mobile County Obstetrical and Gynecological Society. (1949) *President,* O. M. Otts, Jr. *Secretary,* A. K. Conditt, 1367 Government St., Mobile, Ala. Meetings, quarterly when called.

Montgomery County (Ohio) Obstetrical and Gynecological Society. (1937) *President,* L. O. Fredericks. *Secretary,* A. A. Kunnen, 406 Harries Bldg., Dayton, Ohio. Meetings, third Wednesday of each month.

Montana Obstetrical and Gynecological Society. (1946) *President,* B. C. Farrand. *Secretary,* Matthew W. Calvert, Box 427, Laurel, Mont. Next meeting, Billings, Mont., May 2, 1959.

Nashville Obstetrical and Gynecological Society. (1955) *President,* Willard O. Tirrill. *Secretary,* James Ellis, 2122 W. End Ave., Nashville 5, Tenn. Meetings, first Tuesday in each quarter.

Nassau Obstetrical Society. (1944) *President,* Andrew Sherwin. *Secretary,* William F. Finn, 535 Plandome Rd., Manhasset, N. Y. Meetings, second Monday, October, December, February, and April.

New England Obstetrical and Gynecological Society. (1929) *President,* Christopher J. Duncan. *Secretary,* William A. Lynch, 1101 Beacon St., Brookline 46, Mass. Meetings, May and October.

New Haven Obstetrical and Gynecological Society. (1946) *President,* John C. Haley. *Secretary,* David J. Kreis, 59 Trumbull St., New Haven, Conn. Meetings, third Tuesday, September, November, January, March, and May.

New Jersey Obstetrical and Gynecological Society. (1947) *President,* Henry S. Acken, Jr. *Secretary,* Saul B. Gusberg, 180 Fort Washington Ave., New York 32, N. Y. Meetings, second Tuesday, October through May.

New Mexico Obstetrical and Gynecological Society. (1947) *President,* Charles H. Rundles. *Secretary,* Howard L. Smith, 103 N. Pennsylvania, Roswell, N. Mex. Meetings, quarterly.

New Orleans Gynecological and Obstetrical Society. (1924) *President,* C. Gordon Johnson. *Secretary,* Julius T. Davis, Jr., 4414 Magnolia St., New Orleans, La. Meetings, October, November, January, March, and May.

New York Obstetrical Society. (1863) *President,* Henry C. Aken. *Secretary,* S. B. Gusberg, 180 Fort Washington Ave., New York, N. Y. Meetings, second Tuesday, September through May.

North Carolina Obstetrical and Gynecological Society. (1932) *President,* James F. Donnelly. *Secretary,* James A. Crowell, 412 N. Church St., Charlotte 2, N. C. Next meeting, Mid Pines Club, Southern Pines, N. C., April 24-26, 1959.

North Dakota Society of Obstetrics and Gynecology. (1938) *President,* Robert E. Lucy. *Secretary,* G. Wilson Hunter, Fargo Clinic, Fargo, N. D. Meetings, May and September.

Northeastern New York Obstetrical and Gynecological Society. (1935) *President,* Raymond L. Rhodes, Glen Falls, N. Y. *Secretary,* Thomas F. D'Aurio, 17 State St., Troy, N. Y. Meetings, fourth Thursday, January, April, and September.

Northern California Obstetrical and Gynecological Society. (1955) *President,* Donald A. McKinnon. *Secretary,* Nicholas Demas, 127 E. Acacia St., Stockton, Calif. Meetings, second Friday of January, March, June, and October.

Oklahoma City Obstetrical and Gynecological Society. (1940) *President,* Walter K. Hartford. *Secretary,* William L. Bond, 1200 N. Walker, Oklahoma City, Okla. Meetings, February, April, October, and December.

Omaha Obstetrical and Gynecological Society. (1947) *President,* Walter Holden. *Secretary,* W. H. Taylor, Jr., 3807 Cuming St., Omaha 31, Neb. Meetings, third Wednesday, January, March, May, September, and November.

Oregon Society of Obstetricians and Gynecologists. *President,* William O. Thomas, Jr. *Secretary,* Quinten Scherman, 1133 S. W. Market, Portland, Ore. Meetings, third Friday, October through May, except December.

Pacific Coast Obstetrical and Gynecological Society. (1931) *President,* Donald Dallas, San Francisco, Calif. *Secretary,* Richard Reekie, Spokane, Wash. Meeting, St. Francis Hotel, San Francisco, Calif., Oct. 21-24, 1959.

Pacific Northwest Obstetrical and Gynecological Association. (1947) *President,* Alec M. Agnew. *Secretary,* Clifford L. Fearl, 1133 S.W. Market St., Portland 1, Ore. Next meeting, Banff Springs Hotel, Banff, Alberta, Canada, June 20-24, 1959.

Philadelphia, Obstetrical Society of. (1868) *President,* Owen J. Toland. *Secretary,* John P. Emich, Jr., 155 W. Walnut Lane, Philadelphia 44, Pa. Meetings, first Thursday of the month, October through May.

Pittsburgh Obstetrical and Gynecological Society. (1934) *President,* Henry W. Erving. *Secretary,* Joseph Loughrey, 507 Medical Arts Bldg., Fifth and Atwood, Pittsburgh 13, Pa. Meetings, first Monday, October through May, except January.

Portland Society of Obstetricians and Gynecologists. (1928) *President,* William M. Wilson. *Secretary,* David W. James, 4212 N.E. Broadway, Portland 13, Ore. Meetings, fourth Wednesday, September through May.

Queens Gynecological Society. (1948) *President,* Joseph Rich. *Secretary,* B. Edmond Thomas, 30 Grace Ave., Great Neck, N. Y. Meetings, second Wednesday, October, December, February, and April.

Rochester Obstetrical and Gynecological Society. (1939) *President,* John Hamilton. *Secretary,* William Lange, 16 N. Goodman St., Rochester 7, N. Y. Meetings, monthly on Tuesday.

St. Louis Gynecological Society. (1924) *President,* Eugene G. Hamilton. *Secretary,* Ralph Woolf, 630 S. Kingshighway Blvd., St. Louis 10, Mo. Meetings, second Thursday, October, December, February, and April, Congress Hotel.

San Antonio Obstetrical and Gynecological Society. *President,* G. G. Passmore. *Secretary,* Frank M. Posey, Jr., 101 N. McCollough, San Antonio, Texas.

San Diego Gynecological Society. (1937) *President,* Albert P. Kimball. *Secretary,* James R. Phalen, 2850 Sixth Ave., San Diego 3, Calif.

San Francisco Gynecological Society. (1929) *President,* Edmund F. Anderson. *Secretary,* Carl Goetsch, 2915 Telegraph Ave., Berkeley 5, Calif. Meetings, second Friday, October through April.

Seattle Gynecological Society. (1941) *President,* L. Bruce Donaldson. *Secretary,* Robert N. Rutherford, 707 Broadway, Seattle 22, Wash. Meetings, third Wednesday, January, March, April, May, September, October, and November.

South Carolina Obstetrical and Gynecological Society. (1946) *President,* William A. Hart. *Secretary,* Albert J. Baroody, 352 W. Palmetto St., Florence, S. C. Next meeting, fall of 1959.

South Dakota Society of Obstetrics and Gynecology. (1952) *President,* Paul Billingsley. *Secretary,* C. A. Stern, 1320 S. Minnesota Ave., Sioux Falls, S. D. Meetings, June and September.

Southern California, Obstetrical and Gynecological Assembly of. (1945) *President,* Daniel G. Morton, Los Angeles, Calif. *Secretary,* Keith P. Russell, 511 S. Bonnie Brae St., Los Angeles 57, Calif. Next meeting, Los Angeles, Feb. 9-13, 1959.

Southwest Obstetrical and Gynecological Society. (1951) *President,* Donovan Johnson, Santa Ana, Calif. *Secretary,* Zeph B. Campbell, 550 W. Thomas Rd., Phoenix, Ariz. Next meeting, Palm Springs, Calif., November, 1959.

Texas Association of Obstetricians and Gynecologists. (1930) *President,* Jesson L. Stowe, El Paso, Texas. *Secretary,* Oran V. Prejean, 1317 N. Washington Ave., Dallas 4, Texas. Annual meeting, Hotel Texas, Fort Worth, Texas, Feb. 14, 1959.

Tulsa County Obstetrical and Gynecological Society. (1955) *President,* Adolph N. Vammen. *Secretary,* James T. Maddox, 3102 S. Harvard, Tulsa, Okla. Meetings, January, April, May, and in the fall.

Utah Obstetrical and Gynecological Society. (1948) *President,* Lindsay R. Curtis. *Secretary,* E. Conrad Monsen, c/o Ogden Clinic, Ogden, Utah. Meetings second Thursday of October, December, February, and May.

Virginia Obstetrical and Gynecological Society. (1936) *President,* Washington C. Winn. *Secretary,* Brock D. Jones, Jr., 1204 Colonial Ave., Norfolk, Va. Meetings, spring and fall.

Washington Gynecological Society. (1933) *President,* Howard P. Parker. *Secretary,* Robert B. Nelson, Jr., 1824 Massachusetts Ave., N. W., Washington 6, D. C. Meetings, October, December, January, March, and May.

Washington State Obstetrical Association. (1936) *President,* Glen G. Rice. *Secretary,* Donald M. McIntyre, 1420 Seneca St., Seattle 1, Wash. Meetings, April 11, 1959, and in the fall.

West Texas Obstetrical and Gynecological Society. (1954) *President,* Joe L. Cornelison, San Angelo, Texas. *Secretary,* Tom C. Burditt, 1440 N. Third St., Abilene, Texas. Annual meeting in December.

Westchester Obstetrical and Gynecological Society. (1939) *President,* Douglas H. Robertson. *Secretary,* Joshua W. Davies, 28 Hobart St., Bronxville, N. Y. Meetings, second Wednesday of the month.

Wisconsin Society of Obstetrics and Gynecology. (1940) *President,* Ralph E. Campbell, Madison, Wis. *Secretary,* William C. Mussey, 113 N. Carroll Ave., Madison 3, Wis. Spring meeting in conjunction with the Wisconsin State Medical Society.